JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

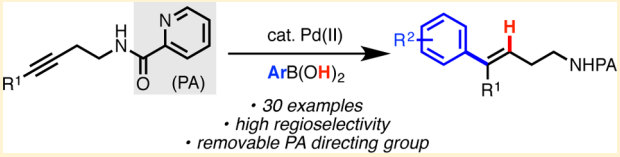
Palladium(II)-Catalyzed Regioselective syn-Hydroarylation of Disubstituted Alkynes Using a Removable Directing Group

Zhen Liu, Joseph Derosa, and Keary M. Engle*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

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.

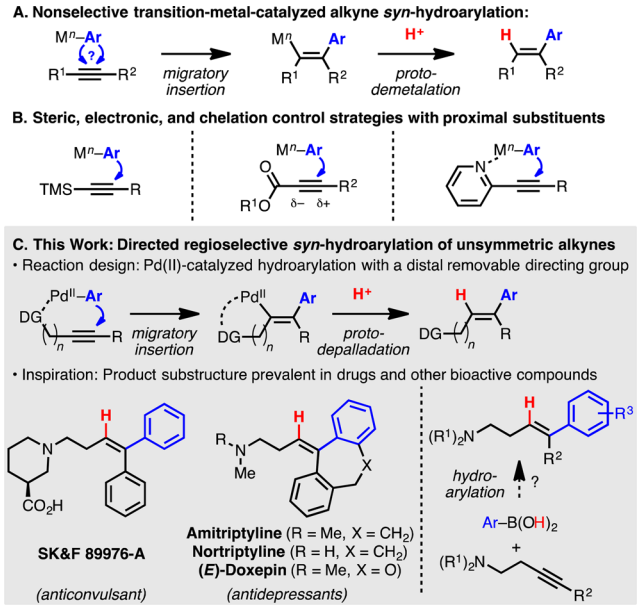


INTRODUCTION

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 co-workers 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/hydropalladation sequence.[5] Since then, transition-metal-catalyzed hydroarylation has emerged as a powerful technique to synthesize di- and trisubstituted alkenes.[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 nonremovable functional groups (e.g., a 2-pyridyl moiety) to improve selectivity through chelation and/or electronic effects (Scheme 1b).[2g,6a,b,f,7a,c,d]

Scheme 1. Background and Project Synopsis



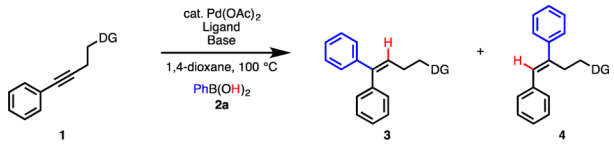
Despite this progress, these strategies possess limitations. First, these reactions can exhibit variable selectivity as the substitution patterns on the arylboronate and alkyne substrate change. Second, they require proximal substituents that can be difficult to modify downstream, which limits overall 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]

Received: August 23, 2016
Published: September 7, 2016

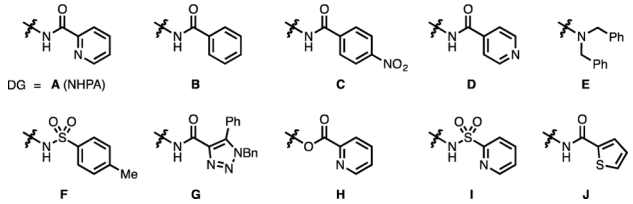
DOI: 10.1021/jacs.6b08818
J. Am. Chem. Soc. 2016, 138, 13076−13081

Table 1. Optimization of the Reaction Conditions[a]



etry	DG	ligand	base	Pd/L (mol %)	3 (%)[b]	4 (%)[b]	selectivity (3/4)[c]
1	A (NHPA)	none	K_2CO_3	–	9	–	–
2	A (NHPA)	(±) BINAP	K_2CO_3	5/5	trace	–	–
3	A (NHPA)	$PCy_3{\cdot}HBF_4$	K_2CO_3	5/10	55	3.7	15:1
4	A (NHPA)	XPhos	K_2CO_3	5/10	34	3.8	8.9:1
5	A (NHPA)	*N*-acetylglycine	K_2CO_3	5/10	29	10	2.8:1
6	A (NHPA)	$PCy_3{\cdot}HBF_4$	KF	5/10	77	12	6.3:1
7	A (NHPA)	$PCy_3{\cdot}HBF_4$	K_3PO_4	5/10	10	2.5	25:1
8	A (NHPA)	$PCy_3{\cdot}HBF_4$	KOAc	5/10	64 (60)	2.1	30:1
9[d]	**A (NHPA)**	**$PCy_3{\cdot}HBF_4$**	**KOAc**	**5/5**	**80 (78)**	–	**>50:1**
10[d]	B	$PCy_3{\cdot}HBF_4$	KOAc	5/5	76	13	5.8:1
11[d]	C	$PCy_3{\cdot}HBF_4$	KOAc	5/5	82	10	8.0:1
12[d]	D	$PCy_3{\cdot}HBF_4$	KOAc	5/5	89	4.9	18:1
13[d]	E	$PCy_3{\cdot}HBF_4$	KOAc	5/5	78	7.1	11:1
14[d]	F	$PCy_3{\cdot}HBF_4$	KOAc	5/5	80	14	5.6:1
15[d]	G	$PCy_3{\cdot}HBF_4$	KOAc	5/5	14	3.5	7.4:1
16[d]	H	$PCy_3{\cdot}HBF_4$	KOAc	5/5	27	3.1	9.6:1
17[d]	I	$PCy_3{\cdot}HBF_4$	KOAc	5/5	74	8.1	9.1:1
18[d]	J	$PCy_3{\cdot}HBF_4$	KOAc	5/5	72	11	6.7:1

[a]Reaction 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, N_2, 4–5 h. [b]Yields were determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. Values in parentheses correspond to isolated yields. [c]Determined by ^1H NMR analysis. [d]90 °C.



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.

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 $PCy_3{\cdot}HBF_4$ as the ligand, trisubstituted alkene **3a** was observed as the major product, with minimal formation of the minor isomer **4a** (**3a**/**4a** = 15:1) (entry 3). The addition of PCy_3 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).

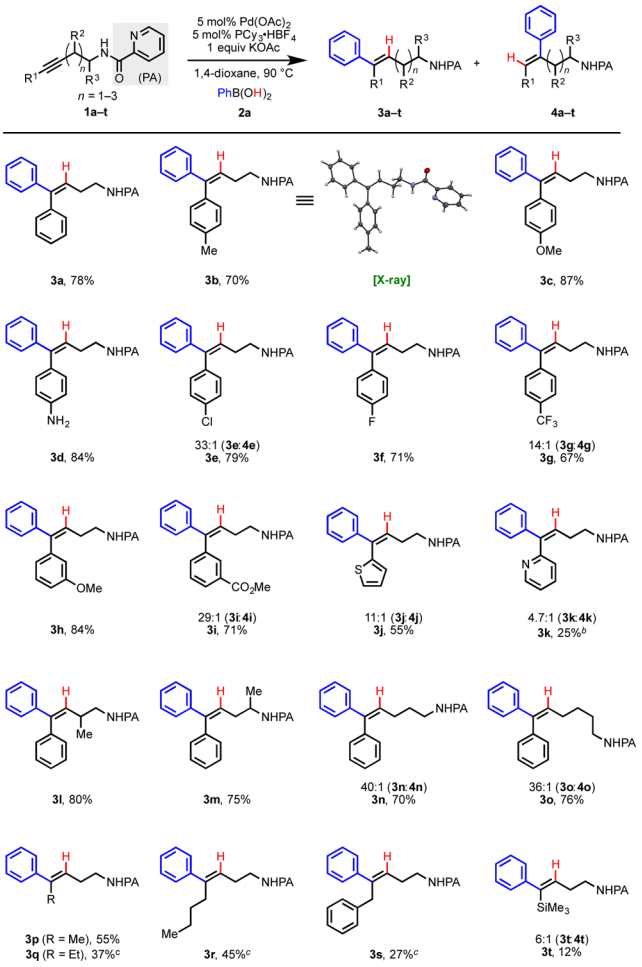
The data from our directing group optimization effort shed light on structure–activity relationships in this reaction (entries 9–18), revealing that both the electronic properties of the auxiliary and the geometry of the metal binding sites significantly impact selectivity. More electron-deficient amides (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

DOI: 10.1021/jacs.6b08818
J. Am. Chem. Soc. 2016, 138, 13076–13081

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.

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

Table 2. Homopropargyl Picolinamide Scope[a]



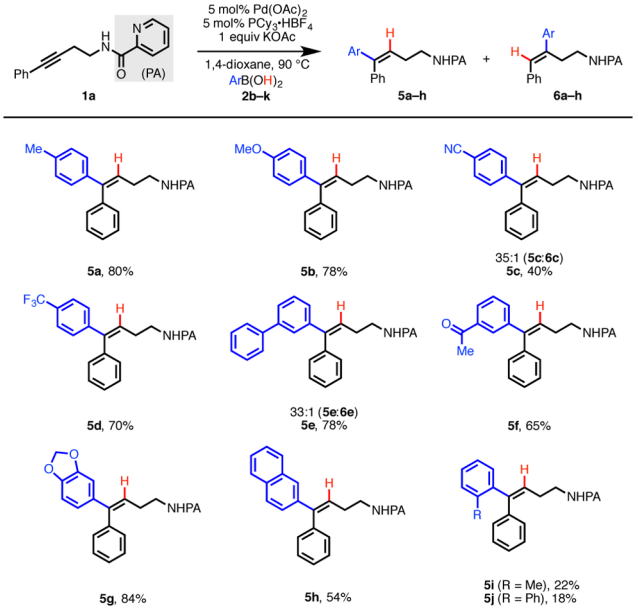
[a]Reaction conditions: **1a–t** (0.1 mmol), **2a** (0.18 mmol), $Pd(OAc)_2$ (5 mol %), $PCy_3{\cdot}HBF_4$ (5 mol %), KOAc (1 equiv), 1,4-dioxane (0.4 mL), 90 °C, N_2, 4–5 h. Percentages represent isolated yields of the major regioisomer. The ratio of the two regioisomers was determined by ^{1}H NMR analysis of the crude reaction mixture. [b]10 mol % $PCy_3{\cdot}HBF_4$. [c]5 mol % PPh_3, 1 equiv of K_2HPO_4, 12–20 h.

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 nondirected 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 $SiMe_3$ group on the alkyne led to 6:1 selectivity, with 12% isolated yield of the major product **3t**.

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

Table 3. Arylboronic Acid Scope[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2b–k** (0.18 mmol), $Pd(OAc)_2$ (5 mol %), $PCy_3{\cdot}HBF_4$ (5 mol %), KOAc (1 equiv), 1,4-dioxane (0.4 mL), 90 °C, N_2, 4–5 h. Percentages represent isolated yields of the major regioisomer. The ratio of the two regioisomers was determined by ^{1}H NMR analysis of the crude reaction mixture.

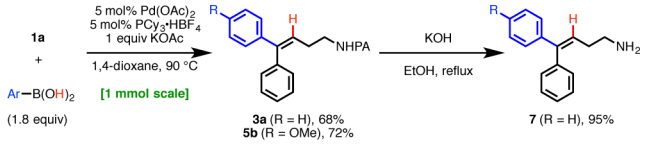
DOI: 10.1021/jacs.6b08818
J. Am. Chem. Soc. 2016, 138, 13076–13081

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 a tool in divergent synthesis for medicinal chemistry applications.

To demonstrate the practicality and operational simplicity of this Pd(II)-catalyzed alkyne hydroarylation method, we performed two representative examples on a larger scale (Scheme 2). Electron-neutral and -rich arylboronic acids were

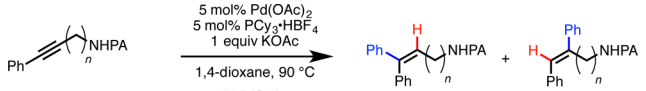
Scheme 2. Large-Scale Synthesis of Trisubstituted Alkenes 3a and 5b and Removal of the Picolinoyl Group



both tested on 1 mmol scale under the reaction conditions described in Tables 2 and 3, 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 basic conditions to give primary amine **7** in 95% yield.

To better understand the influence of the 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

Scheme 3. Comparison of Alkynyl Picolinamides with Different Tether Lengths



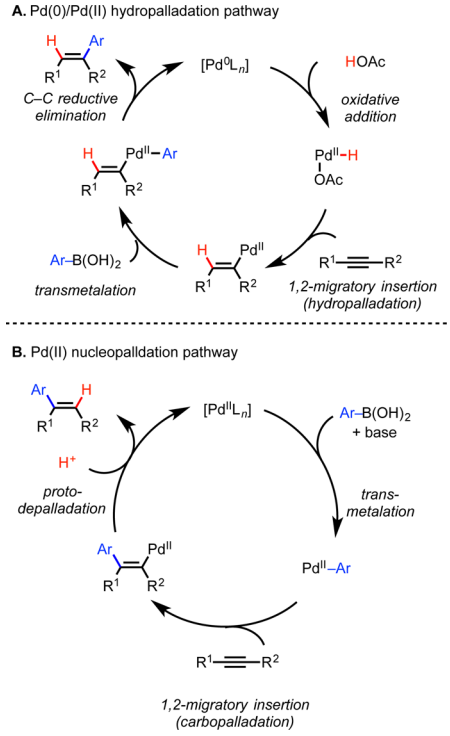
	3 (%)	4 (%)	ratio
$n = 1$	68	23	3:1
$n = 2$	78	<1	>50:1
$n = 3$	70	<2	40:1
$n = 4$	76	~2	36:1

cases that were examined, the reaction proceeded 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 the putative 4-membered palladacycle formed via *syn*-carbopalladation is prohibitively unstable, causing the system to default to more inherent nondirected selectivity. While transition state inductive effects[14] 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.

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

Scheme 4. Comparison of Two Commonly Invoked Mechanistic Paradigms



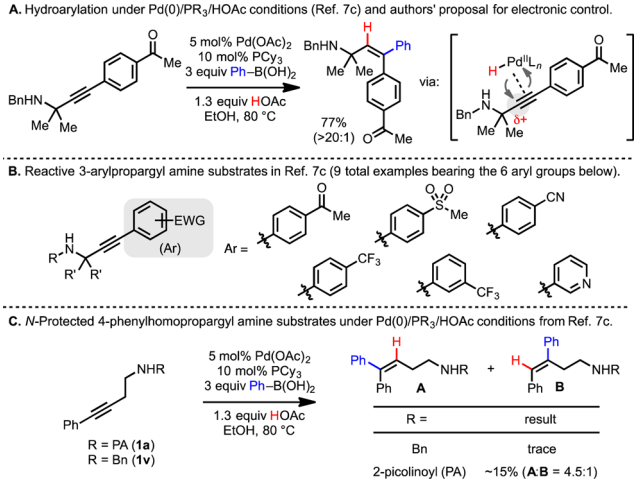
palladium(0) as the catalyst, generally in combination with a phosphine ligand and in an acidic solvent medium (e.g., HOAc) (Scheme 4a).[7a−c,f] To generate the catalytically active species in these systems, a palladium(0) precatalyst, such as $Pd_2(dba)_3$, can be employed directly or a palladium(II) precatalyst, such as $Pd(OAc)_2$, can be reduced in situ. In the proposed sequence of events, the $[Pd(0)L_n]$ species oxidatively adds to HOAc,[15] to generate a $[Pd(II)-H]$ 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 Pd(0), thereby closing the catalytic cycle.

DOI: 10.1021/jacs.6b08818
J. Am. Chem. Soc. 2016, 138, 13076−13081

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 a 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 (Pd(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 Pd(0)/PCy_3/HOAc system, Marinelli and co-workers have previously demonstrated hydroarylation of 3-arylpropargyl amines in 43−85% yield and >20:1 selectivity favoring Ar group transfer to the alkynyl carbon atom distal from the amine (Scheme 5).[7c] The authors report nine

Scheme 5. Relevant Literature Precedent Involving Pd(0)/PCy_3/HOAc Catalysis to Effect Hydroarylation of 3-Arylpropargyl Amines and Attempted Application of this Catalytic System to 4-Arylhomopropargyl Amine Substrates

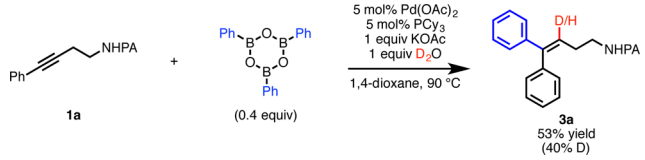


examples, all of which contain electron-withdrawing substituents on the arene. Based on analysis of reactivity trends and computed charge distribution in putative intermediates, the authors conclude that the regioselectivity is due to electronic bias in the alkyne, with the hydride of the [Pd(II)−H] species reliably attacking the alkynyl carbon atom with the highest partial positive charge in the π-alkene complex.[16]

Given that Marinelli's Pd(0)/PCy_3/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-arylproparyl 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

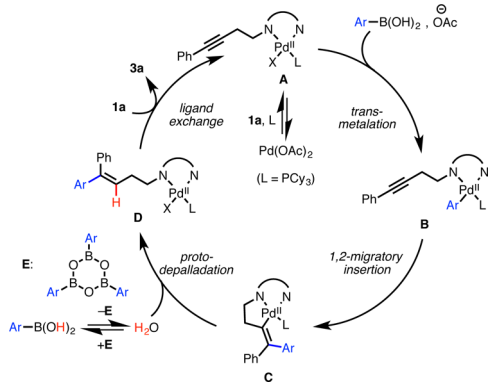
Scheme 6. Deuterium Labeling Study



equiv of D_2O, 40% deuterium was observed exclusively at the vinylic position, with the remaining nondeuterated product presumably arising from the NHPA group. This result is consistent with the vinylic hydrogen in the product originating 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 the 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

Scheme 7. Proposed Reaction Mechanism



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**. The aryl moiety is transferred to alkyne via *syn*-1,2-migratory insertion (carbopalladation) to form bicyclic palladacycle intermediate **C**. Complex **C** reacts via protodepalladation[17] to afford palladium complex **D**. Ligand exchange with a new substrate molecule then releases the product and regenerates 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.

DOI: 10.1021/jacs.6b08818
J. Am. Chem. Soc. 2016, 138, 13076−13081

CONCLUSION

In conclusion, we have reported a regioselective *syn*-hydroarylation of nonsymmetrical 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08818.

Crystallographic data (CIF)
Experiment details, spectra data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data (PDF)

AUTHOR INFORMATION

Corresponding Author

*keary@scripps.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by TSRI and Pfizer, Inc. We thank Prof. Arnold L. Rheingold (UCSD) for X-ray crystallographic analysis.

REFERENCES

(1) For reviews, see: (a) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002. (b) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(2) For organosilane reagents, see: (a) Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* **2002**, 295. (b) Lin, B.; Liu, M.; Ye, Z.; Zhang, Q.; Cheng, J. *Tetrahedron Lett.* **2009**, *50*, 1714. For organostannane reagents, see: (c) Oda, H.; Morishita, M.; Fugami, K.; Sano, H.; Kosugi, M. *Chem. Lett.* **1996**, *25*, 811. (d) Fugami, K.; Hagiwara, S.; Oda, H.; Kosugi, M. *Synlett* **1998**, 477. For organomagnesium reagents, see: (e) Yamagami, T.; Shintani, R.; Shirakawa, E.; Hayashi, T. *Org. Lett.* **2007**, *9*, 1045. For organozinc reagents, see: (f) Murakami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2009**, *11*, 2373. For organolithium reagents, see: (g) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621. For organocopper reagents, see: (h) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098.

(3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(4) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918.

(5) Oh, C. H.; Jung, H. H.; Kim, K. S.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805.

(6) For rhodium-catalyzed hydroarylation of alkynes with boronic acids, see: (a) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123. (b) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762. (c) Genin, E.; Michelet, V.; Genêt, J.-P. *J. Organomet. Chem.* **2004**, *689*, 3820. (d) Genin, E.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4157. (e) Zhang, W.; Liu, M.; Wu, H.; Ding, J.; Cheng, J. *Tetrahedron Lett.* **2008**, *49*, 5214. (f) Gourdet, B.; Smith, D. L.; Lam, H. W. *Tetrahedron* **2010**, *66*, 6026.

(7) For palladium-catalyzed hydroarylation of alkynes with boronic acids, see: (a) Kim, N.; Kim, K. S.; Gupta, A. K.; Oh, C. H. *Chem. Commun.* **2004**, 618. (b) Gupta, A. K.; Kim, K. S.; Oh, C. H. *Synlett* **2005**, 457. (c) Arcadi, A.; Aschi, M.; Chiarini, M.; Ferrara, G.; Marinelli, F. *Adv. Synth. Catal.* **2010**, *352*, 493. (d) Rodriguez, A.; Moran, W. J. *Lett. Org. Chem.* **2010**, *7*, 7. (e) Xu, X.; Chen, J.; Gao, W.; Wu, H.; Ding, J.; Su, W. *Tetrahedron* **2010**, *66*, 2433. (f) Yang, Y.; Wang, L.; Zhang, J.; Jin, Y.; Zhu, G. *Chem. Commun.* **2014**, *50*, 2347.

(8) For other transition-metal-catalyzed hydroarylation reaction of alkynes with boronic acids, see: (a) Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2001**, 2688. (b) Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010. (c) Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chem. - Eur. J.* **2008**, *14*, 11296. (d) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423.

(9) Under certain hydroarylation conditions, selective aryl addition at the β position of 1-phenylpropyne has also been observed. See: refs 7c, 7d, and 7e.

(10) For a review, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. For selected examples of directed carbometalation, see: (b) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (c) Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764.

(11) For selected examples of drug molecules containing a 4,4-diaryl homoallylic amine motif, see: (a) Borden, L. A.; Dhar, T. G. M.; Smith, K. E.; Weinshank, R. L.; Branchek, T. A.; Gluchowski, C. *Eur. J. Pharmacol., Mol. Pharmacol. Sect.* **1994**, *269*, 219. (b) Barbui, C.; Hotopf, M. *Br. J. Psychiatry* **2001**, *178*, 129. (c) Prochazka, A. V.; Weaver, M. J.; Keller, R. T.; Fryer, G. E.; Licari, P. A.; Lofaso, D. *Arch. Intern. Med.* **1998**, *158*, 2035. (d) Fulton-Kehoe, D.; Rossing, M. A.; Rutter, C.; Mandelson, M. T.; Weiss, N. S. *Br. J. Cancer* **2006**, *94*, 1071.

(12) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(13) In some cases, trace amounts of the *anti*-hydroarylation regioisomers were formed. However, in all cases these were observed in less than 3% yield.

(14) (a) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960. (b) Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 6703.

(15) For selected examples of $[Pd(0)L_n]$ oxidative addition to carboxylic acids to form [Pd(II)−H] species, see: (a) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. (b) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. (c) Konnick, M. M.; Gandhi, B. A.; Guzei, I. A.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904.

(16) The authors in ref 7c also demonstrate that the opposite regioisomer is preferentially formed under alternate reaction conditions using a Rh(I) catalyst. In this case the regioselectivity is also proposed to be rooted in electronic effects, with the Rh(I)−Ar intermediate attacking the more electropositive alkynyl carbon atom.

(17) For selected examples of protonolysis of alkenyl C−Pd bonds, see: (a) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (b) Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2123. (c) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (d) Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2011**, *13*, 4858. (e) Zhu, G.; Chen, Y.; Wang, Y.; Zheng, R. *Chem. Commun.* **2012**, *48*, 5796.

DOI: 10.1021/jacs.6b08818
J. Am. Chem. Soc. 2016, 138, 13076−13081