Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Palladium-Catalyzed Three-Component-Coupling Strategy for the Differential Vicinal Diarylation of Terminal 1,3-Dienes

Benjamin J. Stokes, Longyan Liao, Aline Mendes de Andrade, Qiaofeng Wang, and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

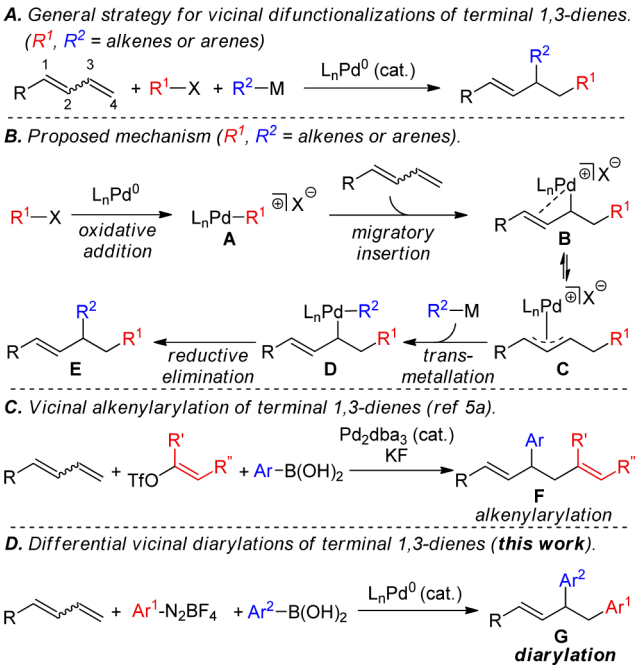
Supporting Information

ABSTRACT: A palladium-catalyzed intermolecular vicinal diarylation of terminal 1,3-dienes using aryldiazonium tetrafluoroborates and arylboronic acids is reported. Using this technology, two different arenes are regioselectively introduced in a vicinal fashion across the terminal alkene of a variety of terminal 1,3-dienes at ambient temperature. Through the action of a chiral bicyclo[2.2.2]octadienyl ligand at −20 °C, good enantioselectivity has also been achieved.

A number of intermolecular alkene diarylation reactions have been developed wherein 2 equiv of a single arene are added to an alkene in a single step.[1] Consequently, two identical aryl groups are incorporated. In the interest of rapidly generating complexity from simple feedstock starting materials, there is a strong desire to develop single-step alkene diarylation reactions wherein *different* arenes are added across an alkene selectively in the presence of a palladium catalyst. While norbornadiene,[2] terminal allenes,[3] and more recently simple terminal alkenes[4] have been used as substrates in three-component diarylations, selective three-component diarylations of terminal 1,3-dienes are not yet known. Three-component couplings of terminal 1,3-diene substrates attracted our interest because, unlike the aforementioned technologies, we envisioned that the products could retain an alkene functional group and also incorporate a chiral center.

Our approach to the vicinal difunctionalization of terminal 1,3-dienes is shown in Scheme 1A. Mechanistically, such reactions are initiated upon oxidative addition of an sp^2 carbon electrophile to Pd(0). This generates a cationic Pd-alkyl species **A** that may undergo migratory insertion and defer transmetalation if the leaving group is noncoordinating (Scheme 1B).[5] The resultant Pd-alkyl **B** is stabilized as a π-allyl **C** that resists β-hydride elimination.[6] To complete the difunctionalization sequence, transmetalation and reductive elimination of the second sp^2 coupling partner, R^2, affords the product **E**. This strategy was implicated in our previous vicinal alkenylarylation of 1,3-dienes, which gave products of the type **F** (Scheme 1C).[5a] Unfortunately, our attempts to develop an analogous three-component diarylation by using aryl triflates instead of alkenyl triflates consistently failed, which is likely a result of the relative inertia of aryl triflates.[7] We now wish to report the successful development of a three-component vicinal diarylation of 1,3-dienes, which employs aryldiazonium tetrafluoroborates and aryl boronic acids as coupling partners, affording products of type **G** (Scheme 1D). We have also identified a chiral bicyclo[2.2.2]octadienyl ligand that is capable of delivering diarylation products with good levels of enantiomeric enrichment.

Scheme 1. Three-Component-Couplings of Terminal 1,3-Dienes

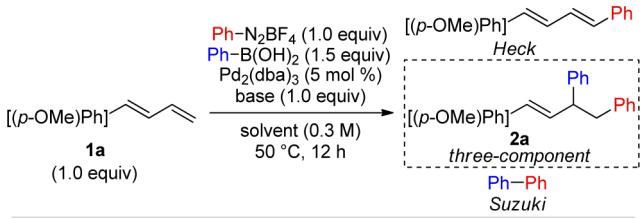


We began the study by optimizing the coupling of *trans*-1-(*para*-methoxyphenyl)-1,3-butadiene **1a** with phenyldiazonium tetrafluoroborate and phenylboronic acid (Table 1). Arenediazonium tetrafluoroborates were chosen not only because they readily oxidize Pd(0) but also because they afford the aforementioned requisite cationic aryl-Pd intermediates required for migratory insertion (see **A** in Scheme 1B).[4,8] Starting with our previously reported alkenylarylation conditions,[5a] the indicated Heck product predominated over both the desired vicinal diarylation product **2a** and the Suzuki product (entry 1).

Received: July 31, 2014
Published: August 27, 2014

   dx.doi.org/10.1021/ol502279u | *Org. Lett.* 2014, 16, 4666−4669

Table 1. Optimization of the Three-Component-Coupling of 1a with Phenyl Diazonium Tetrafluoroborate and Phenyl Boronic Acid



entry	base	solvent	conv (%)[a] of **1a**	yield (%)[a] of **2a**	selectivity[a] (**2a**/Suzuki/Heck)
1	KF	DMA	70	8	04:04:92
2	KF	1,4-dioxane	100	14	50:50:tr
3	KF	THF	100	tr	tr:50:50
4	KF	MeOH	100	tr	tr:08:92
5	KF	EtOH	100	4	05:19:76
6	KF	*i*-PrOH	100	11	14:14:72
7	KF	*t*-BuOH	100	33	62:13:25
8	KF	*t*-AmylOH	93	53	92:02:06
9[b]	KF	*t*-AmylOH	90	57	94:03:03
10[b]	$NaHCO_3$	*t*-AmylOH	96	58	96:02:02
11[b,c]	$NaHCO_3$	*t*-AmylOH	100	80	94:04:02

[a]Determined by GC analysis using dodecane as an internal standard following response factor correction. [b]This reaction was conducted at room temperature. [c]An additional 15 mol % of dba was added to this reaction.

In contrast to *N*,*N*-dimethylacetamide (DMA), 1,4-dioxane minimized Heck product formation but afforded an equimolar ratio of **2a** and the Suzuki product (entry 2). Interestingly, another ethereal solvent, THF, afforded only trace amounts of **2a** and an equimolar ratio of Suzuki and Heck products (entry 3). Next, alcoholic solvents, which have proven valuable in differential geminal diarylations of terminal alkenes with diazonium salts and boronic acids,[4] were examined. While trace amounts of **2a** and mostly the Heck product were observed in methanol (entry 4), increasingly bulky alcohols led to improved yields of **2a** at the expense of the Heck product (entries 4–8). In particular, the use of *tert*-amyl alcohol afforded superior selectivity for the desired diarylation product over both Heck and Suzuki products (entry 8). Comparable results were obtained when the reaction was carried out at ambient temperature (entry 9) and with $NaHCO_3$ in place of KF (entry 10). The final breakthrough was the addition of exogenous dibenzylideneacetone (dba), which improved the yield significantly, presumably by preventing the detrimental accrual of unligated Pd(0) (entry 11).[9,10]

Under the optimized conditions, we initially investigated increasingly electron-deficient *trans*-1-phenyl-1,3-butadienes **1b** and **1c** in order to directly compare 1-aryl-1,3-diene electronic effects on vicinal diarylations (Figure 1). These substrates afforded diminishing yields of the corresponding 1,3,4-triaryl-1-butene products **2b** (65%) and **2c** (52%), although the selectivity for the difunctionalization product remained >95% in these cases and all subsequent ones. Next, *trans*-1-(*para*-fluorophenyl)-1,3-butadiene **1d** was found to react efficiently with *para*-methoxyphenyldiazonium tetrafluoroborate and phenylboronic acid, affording an 83% yield of **2d**. Additionally, the reaction between (*E*)-1-(1-naphthyl)-1,3-butadiene, 4-nitrophenyldiazonium tetrafluoroborate, and phenyl boronic acid delivered the designated nitrophenyl-containing product **2e** in 50% yield.

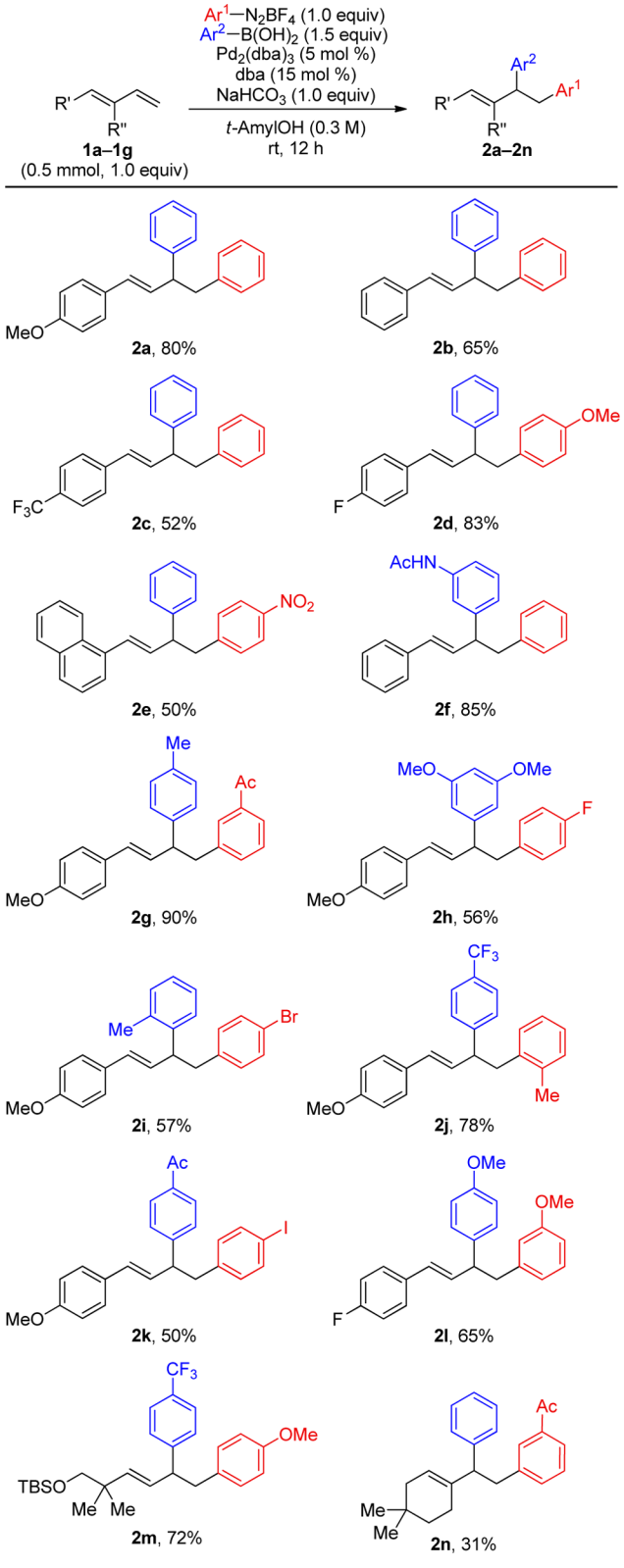


Figure 1. Exploration of the scope of coupling partners in the three-component diarylation of terminal 1,3-butadienes. The isolated yield of each product is reported.

Having established the broad tolerance of electronically disparate terminal 1,3-dienes and phenyldiazonium salts in **2a**–

dx.doi.org/10.1021/ol502279u | *Org. Lett.* 2014, 16, 4666–4669

2e, we turned our attention to functional group compatibility. In addition to the aforementioned methylphenyl ether (**2a**), trifluoromethylphenyl (**2c**), fluorophenyl (**2d**), and nitrophenyl (**2e**) functional groups, a phenylacetamide group was introduced to the substrate via the boronic acid component, giving **2f** in high yield. Functionalized phenyldiazonium salts and phenylboronic acids also could be incorporated simultaneously, with installation of the diazonium component in the homallylic position and the boronic acid component in the allylic position of the product, as shown in **2g**–**2l**. In addition to the use of trifluoromethyl (**2c** and **2h**), fluoro (**2d** and **2h**), and nitro (**2e**) arene substituents, other functional groups that are well-tolerated include a ketone (**2g** and **2k**), an aryl bromide (**2i**), and even an aryl iodide (**2k**) in reactions with 1-(*para*-methoxyphenyl)-1,3-butadiene.

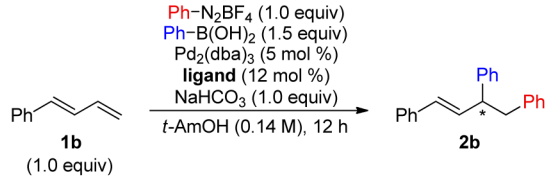
With respect to the phenylboronic acid component, both electron-rich and -poor examples are well-tolerated (compare, for example, *para*-CF_3-containing product **2j** and *para*-OMe-containing product **2l**). The boronic acid can also be sterically hindered, as an *ortho*-tolyl group can be added to the allylic position (see **2i**). Conversely, *ortho*-tolyldiazonium tetrafluoroborate can be used to install the group in the homoallylic position (**2j**).[11]

Alkyl 1,3-dienes were also tested as substrates under the optimized conditions. To this end, a protected alcohol-containing 1,3-diene coupled efficiently to *para*-methoxyphenyl and *para*-(trifluoromethyl)phenyl groups, giving **2m**. In contrast, a trisubstituted alkene-containing substrate afforded a diminished yield of **2n** when coupled to the indicated arenes. These results are consistent with the requirement of a large substituent at the 1-position of the 1,3-diene to avoid $\sigma-\pi-\sigma$ isomerization of the Pd-allyl intermediate (**C**, Scheme 1), which would afford 1,4-diarylation products.[12] These examples, combined with those of **2a**–**2l**, make clear that a wide variety of electronically and sterically diverse 1,3-dienes and arenes may be combined under these conditions.

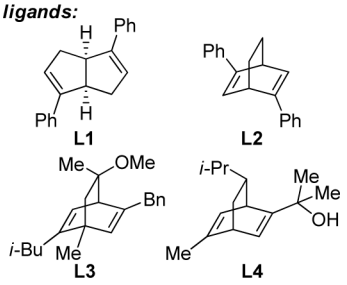
The development of a catalytic enantioselective route to the diarylation products **2** is of interest because these products are precursors to pharmaceutically important enantioenriched α-arylpropionic acids,[13] and their asymmetric synthesis has not yet been achieved.[14] Thus, a catalytic asymmetric route starting from terminal 1,3-dienes, which are prepared in one step, would streamline the access to enantioenriched variants of **2**. We therefore sought to identify a suitable chiral ligand that would deliver **2** in high enantiomeric excess (ee) and yield. Unfortunately, the addition of privileged nucleophilic ligands for cross-coupling reactions, such as phosphines (including phosphoramidites), N-heterocyclic carbenes, and bidentate amines, afforded Suzuki cross-coupling as the major reaction outcome; the diene substrates were not consumed (see the Supporting Information for details). This may be due to the fact that Lewis basic ligands change the electrophilic nature of the Pd-alkenyl adduct (intermediate **A**, Figure 1) so as to favor transmetalation over alkene insertion. This problem is encountered in all of our three-component-coupling methods (sp^2–sp^2 Suzuki coupling partners are present but must not react with one another) and is the likely reason why each of these optimized reactions perform best under "ligandless" conditions.[5]

Given that dba, an achrial diene, is well-tolerated in each of our three-component-coupling reactions, we looked to commercially available chiral dienes for suitability as non-nucleophilic ligands[15] (although it should be noted that the substrate is itself a diene, which may confound effective asymmetric catalysis). Under the optimized conditions identified in Table 1 above, tetrahydropentalenyl ligand **L1** afforded 1,3,4-triphenyl-1-butene **2b** in just 3% enantiomeric excess (Table 2, entry 1). A substantial improvement was

Table 2. Selected Ligand and Temperature Effects on Asymmetric Induction in the Vicinal Diphenylation of (*E*)-1-Phenyl-1,3-butadiene



entry	temp. (°C)	ligand	yield (%)[a]	ee (%)[b]
1	rt	**L1**	n.d.	3
2	rt	**L2**	n.d.	29
3	rt	**L3**	n.d.	51
4	rt	**L4**	n.d.	65
5	–8	**L4**	10	83
6	0	**L4**	33	80
7	40	**L4**	51	55



[a]Determined by GC analysis using dodecane as an internal standard following response factor correction. [b]Determined by SFC analysis.

observed through the use of bicylo[2.2.2]octadienyl ligand **L2**, which afforded **2b** in 29% ee (entry 2). Focusing on the bicyclo[2.2.2]octadienyl core, we found that the pseudo C_2-symmetric (*R*)-(−)-carvone-derived ligand **L3** delivered **2b** in 51% ee (entry 3), while (*R*)-(−)-α-phellandrene-derived **L4** performed the best under these conditions, affording a promising 65% ee (entry 4).[16] A brief temperature profile revealed that the enantioselectivity could be improved by decreasing the temperature, albeit at the expense of the reaction yield. At −8 °C, just above the freezing point of *tert*-AmylOH, 83% ee was observed, albeit with a low 10% yield of **2b** (entry 5). Conversely, increasing the temperature to 40 °C resulted in an improved yield (51%) but a diminished ee (55%, entry 7).

Our final aim was to improve the yield of the asymmetric diphenylations using **L4** while preserving enantiomeric excesses. To this end, 1,2-dichloroethane (DCE) was selected as the solvent, enabling the reaction to be carried out at −20 °C, while a slight excess of 1,3-diene substrates and increases in catalyst, ligand, and base loading were also employed (Figure 2). Under these conditions, terminal dienes **1a**–**1c** could be converted to the corresponding (*R*) enantiomers[17] in 75–82% ee and in isolated yields of 25–30%. Neither the yield nor the selectivity was found to depend significantly on the electronic nature of the diene, with electron-rich (**1a**), electron-neutral (**1b**), and electron-deficient (**1c**) substrates behaving similarly. This asymmetric variant resisted our best efforts to increase the yield by changing the conditions or the technical procedure.

In summary, we have developed a highly regioselective vicinal diarylation reaction of terminal 1,3-dienes that incorporates two different aryl groups from diazonium salts and boronic acids. The reaction is conducted under mild conditions, incorporates a variety of functionalized arenes, and can be rendered enantioselective through the use of a chiral bicyclo[2.2.2]octadienyl ligand, albeit in low yield. New

dx.doi.org/10.1021/ol502279u | *Org. Lett.* 2014, 16, 4666–4669

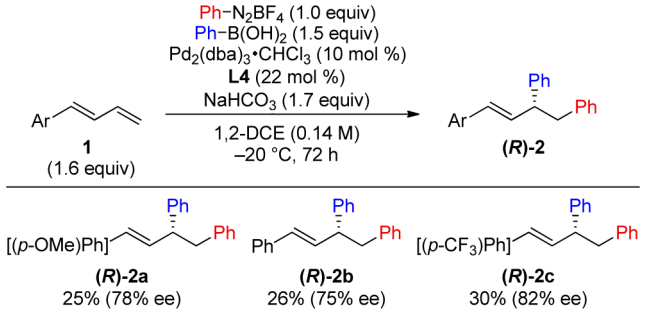


Figure 2. Reoptimized enantioselective diphenylations of (*E*)-1-aryl-1,3-dienes at −20 °C. The isolated yield and enantiomeric excess (as determined by SFC) for each product are reported.

approaches to asymmetric three-component-coupling reactions are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimetal procedures, full spectroscopic data for new compounds, and chiral separations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sigman@chem.utah.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research reported in this publication was supported by the National Institute of General Medical Science of the National Institutes of Health under Award Numbers R01GM063540 and F32GM099254 (B.J.S.), and a Science Without Borders undergraduate scholarship from the National Council for Scientific and Technological Development of Brazil (CNPq) to A.M.A.

■ REFERENCES

(1) (a) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (b) Svennebring, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 3345. (c) Botella, L.; Nájera, C. *J. Org. Chem.* **2005**, *70*, 4360. (d) Zou, G.; Huang, W.; Xiao, Y.; Tang, J. *New J. Chem.* **2006**, *30*, 803. (e) Urkalan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146. (f) Trejos, A.; Fardost, A.; Yahiaoui, S.; Larhed, M. *Chem. Commun.* **2009**, 7587. (g) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett.* **2010**, *12*, 2848. (h) Xu, D.; Lu, C.; Chen, W. *Tetrahedron* **2012**, *68*, 1466.

(2) Oda, H.; Ito, K.; Kosugi, M.; Migita, T. *Chem. Lett.* **1994**, *23*, 1443.

(3) Huang, T.-H.; Chang, H.-M.; Wu, M.-Y.; Cheng, C.-H. *J. Org. Chem.* **2001**, *67*, 99.

(4) Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008.

(5) For alkene insertions into cationic Pd−C_{sp2} intermediates in the presence of transmetallating reagents, see: (a) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784. (b) Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372. (c) McCammant, M. S.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4167. (d) Reference 4.

(6) For a review on the strategic control of *β*-hydride elimination in Pd-catalyzed alkene functionalization reactions, see: DeLuca, R. J.; Stokes, B. J.; Sigman, M. S. *Pure Appl. Chem.* **2014**, *86*, 395.

(7) Elevated temperatures and phosphine ligands are typically required to oxidize Pd(0) with aryl triflates in nonpolar solvents. For leading references, see: (a) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810. (b) Alcazar-Roman, L. M.; Hartwig, J. F. *Organometallics* **2002**, *21*, 491. (c) Jutand, A.; Negri, S. *Organometallics* **2003**, *22*, 4229.

(8) For a review, see: (a) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, *2011*, 1403. For leading references, see: (b) Callonnec, F. o. L.; Fouquet, E.; Felpin, F. o.-X. *Org. Lett.* **2011**, *13*, 2646. (c) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692. (d) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. (e) Oliveira, C. C.; Angnes, R. A.; Correia, C. R. D. *J. Org. Chem.* **2013**, *78*, 4373. (f) Oger, N.; Le Callonnec, F.; Jacquemin, D.; Fouquet, E.; Le Grognec, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2014**, *356*, 1065.

(9) The addition of exogenous dba has been effective in improving yields in alkene difunctionalization reactions. See: Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372.

(10) Geminal diarylation was not observed in these studies.

(11) NMR NOE analyses of **2i** and **2j**, in which the phenyl methyl group of each product was irradiated, confirmed the diazonium-derived arene is installed at the homoallylic position, while the boronic acid derived arene is installed at the allylic position.

(12) For a study of the steric inhibition of $\sigma-\pi-\sigma$ isomerization of similar Pd-allyl intermediates, see: Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 10209.

(13) For example, see: Thalén, L. K.; Sumic, A.; Bogár, K.; Norinder, J.; Persson, A. K. Å.; Bäckvall, J.-E. *J. Org. Chem.* **2010**, *75*, 6842.

(14) Stereospecific palladium-catalyzed arylations of enantiomerically enriched secondary styrenyl carbonates are challenging when a homostyrenyl arene is present because the carbonate is easily eliminated to give 1,4-diaryl-1,3-dienes. See: Zhao, J.; Ye, J.; Zhang, Y. J. *Adv. Synth. Catal.* **2013**, *355*, 491.

(15) For a review on the use of chiral olefins as ligands in asymmetric transition metal catalysis, see: Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

(16) Ligand **L4** was used as purchased from Sigma-Aldrich (product # 723673).

(17) The (*R*) configuration was assigned by converting **(*R*)-2c** into a compound of known absolute configuration, namely 2,3-diphenylpropanoic acid, using an oxidative cleavage reaction. See the Supporting Information for details.