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A Palladium-Catalyzed Three-Component Cross-Coupling of Conjugated Dienes or Terminal Alkenes with Vinyl Triflates and Boronic Acids

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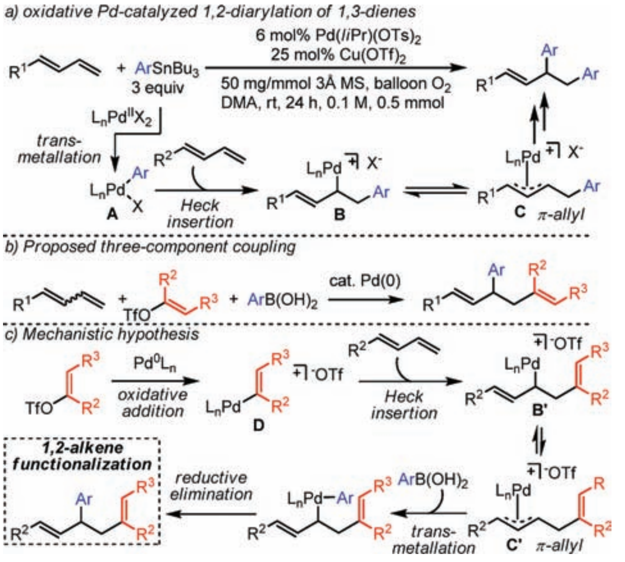
S *Supporting Information*

ABSTRACT: A three-component coupling of vinyl triflates and boronic acids to alkenes catalyzed by palladium is reported. Using 1,3-dienes, selective 1,2-alkene difunctionalization is observed, whereas the use of terminal alkenes results in 1,1-alkene difunctionalization. The reaction outcome is attributed to the formation of stabilized, cationic Pd-π-allyl intermediates to regulate β-hydride elimination.

Significant effort has been afforded to the development of high utility methods involving palladium-catalyzed alkene functionalization as highlighted by the Heck reaction[1] and the Wacker oxidation.[2] Inspired by the key mechanistic motifs of these fundamental reactions, a focus of our research program over the past several years has been the advancement of palladium-catalyzed alkene difunctionalization reactions with the ultimate goal of selectively introducing two groups across the alkene.[3−7] As a specific example, we have reported the diarylation[4c,d] of conjugated and terminal alkenes using oxidative palladium catalysis (Scheme 1a). In this reaction, two aryl groups originating from an arylstannane are added across a 1,3-diene (or styrene) to yield the 1,2-diarylation product. Mechanistically, this reaction is thought to initiate by transmetalation to form Pd-aryl species **A**, Heck insertion of a conjugated diene yielding **B**, and stabilization of the Pd-alkyl as a π-allyl **C**. Subsequent cross-coupling of a second equivalent of an aryl stannane results in product formation.[4d] The success of this reaction is partially attributed to stabilization of the electrophilic Pd-species by formation of either a π-allyl (for dienes)[8] or a π-benzyl (for styrenes)[4c,d,9] intermediate suppressing β-hydride elimination. The obvious synthetic limitation of this 1,2-alkene difunctionalization reaction is the introduction of two identical aryl groups from the arylstannane as well as reasonably complex reaction conditions.[4d]

To overcome this significant synthetic drawback, we considered an alternative and perhaps simpler approach. Specifically, the use of Pd(0) initiated catalysis is proposed wherein a vinyl triflate undergoes oxidative addition to yield Pd-vinyl species **D**. Heck insertion of a diene should produce intermediate **B′** which is closely related to the proposed intermediate in the oxidative Pd-catalyzed diarylation reaction and should be stabilized by formation of a π-allyl **C′** to suppress β-hydride elimination. It should be noted that vinyl triflates were specifically selected to initiate the catalysis since highly electrophilic Pd-species should result in alkene insertion in preference to the more common Suzuki coupling sequence.[10] To complete the process, transmetalation of a boronic acid derivative and reductive elimination will introduce two *different* groups into the alkene framework to yield skipped diene products.[11]

Scheme 1. Proposed Three-Component Coupling of Conjugated Dienes with Vinyl Triflates and Aryl Boronic Acids



Reports of related three-component coupling reactions of this type with Pd have been generally limited to substrates that are unable to undergo β-hydride elimination after Heck insertion such as norbornenes,[12] alkynes,[13] and carbene precursors.[14] Allenes as the "alkene" coupling partner have been reported, where a Pd-π-allyl species is directly formed via migratory insertion to presumably avoid β-hydride elimination in a manner similar to our proposal.[15] Herein, we present the successful development of a three-component coupling[16] to achieve the formation of two sp^2−sp^3 carbon−carbon bonds from the alkene framework using vinyl triflates as the organic electrophile and boronic acids as the organometallic reagent. Surprisingly, this complexity generating reaction occurs under very simple and mild reaction conditions, where alkene 1,2-difunctionalization is achieved using conjugated dienes. Extension to more challenging terminal alkenes, which has not previously been reported, is also presented, yielding the 1,1-alkene difunctionalization products under identical reaction conditions.

For optimization, vinyl triflate **1a**, diene **2a**, and boronic acid **3a** were selected (Table 1). Gratifyingly, the optimized conditions

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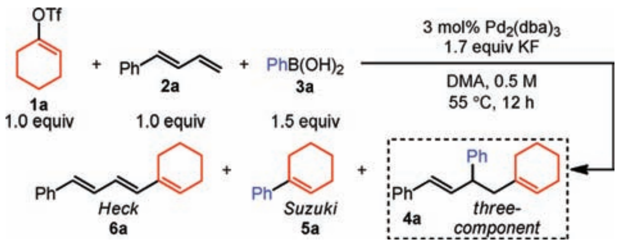
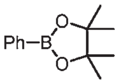
are simple, in which catalytic amounts of $Pd_2(dba)_3$ in the presence of stoichiometric KF as base in dimethylacetamide (DMA) as solvent are required for selective formation of the three-component coupling product **4a**. Other bases, such as K_2CO_3, Cs_2CO_3, and K_3PO_4, also gave the desired product in similar yields, and the addition of exogenous water does not impact the overall outcome of this reaction (see Supporting Information). No added ligand is necessary, implicating to us the importance of solvent acting as a ligand on Pd.[17] Exploration of other solvents highlights this point revealing that common amide solvents (entries 4 and 5) lead to better selectivity for **4a** than other polar solvents such as *tert*-amyl alcohol (entry 2) and DMSO (entry 3) wherein both Heck and Suzuki products are formed in substantial amounts. Addition of several monodentate phosphine ligands (entries 6 and 7) also leads to mixtures of products. Of note, the use of tricyclohexylphosphine promotes the Heck reaction while also forming the diene hydroarylation product, presumably from a Pd-hydride formed in the reaction.[8i] The reaction temperature modestly affects the reaction outcome (entries 8 and 9), while the use of either boronic esters (entry 10) or trifluoroborates (entry 11) leads to lower yields of **4a**. A 1:1 ratio of alkene and vinyl triflate is required to achieve excellent yields of the desired skipped diene products with only a modest excess of the boronic acid.

Table 1. Initial Evaluation of the Three-Component Coupling of 1a, 2a, and 3a To Form 4a

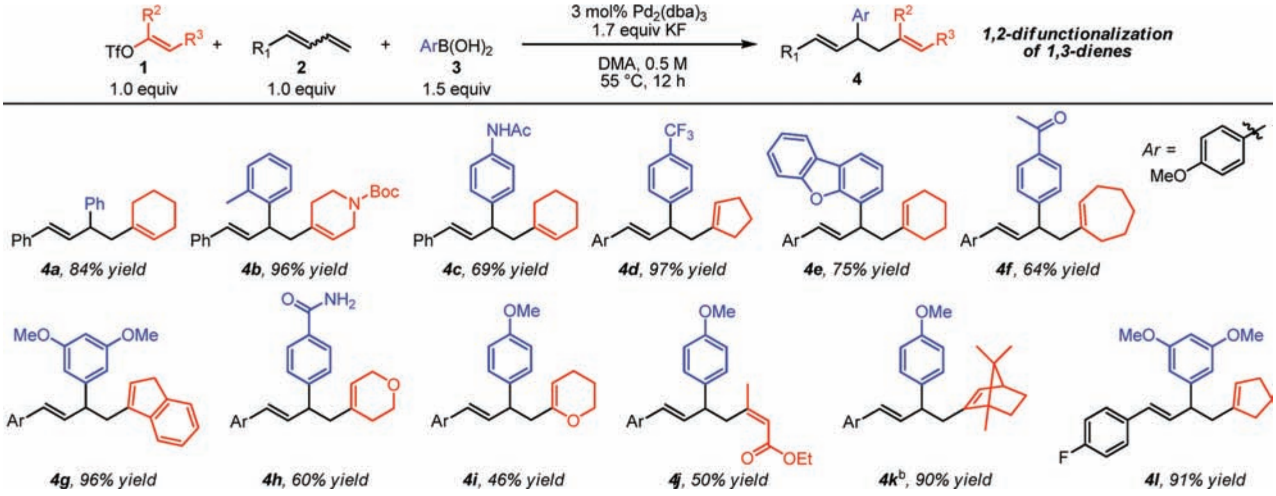


Entry	Changes	% Conv.[a]	%4a[b]	4a : 5a : 6a
1	standard conditions	100	90	> 99% of 4a
2	^{t}AmylOH (solvent)	63	29	71 : 3 : 26
3	DMSO (solvent)	95	21	20 : 10 : 70
4	NMP (solvent)	100	78	> 99% of 4a
5	DMF (solvent)	100	85	> 99% of 4a
6	7 mol% $P(o\text{-tol})_3$	50	14	17 : 67 : 17
7[c]	7 mol% $P(Cy)_3$	100	10	20 : <1 : 80
8	R.T.	99	53	90 : 7 : 3
9	80 °C	98	77	93 : 5 : 2
10[d]		100	40	33 : <1 : 67
11[e]	$PhBF_3K$	20	10	75 : <1 : 25

[a] Conversion of **2a**, measured by GC using an internal standard. [b] GC yield using an internal standard. [c] Hydroarylation product (*E*)-but-1-ene-1,3-diyldibenzene was found in 50% GC yield. [d] 3.0 equiv of 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane were added instead of $PhB(OH)_2$. [e] 3.0 equiv of $PhBF_3K$ were added instead of $PhB(OH)_2$.

Using the standard conditions, we explored the scope of the three-component coupling of 1,3-dienes (Table 2). Previous results from our lab suggested that selective 1,2-addition reactions in the cross-coupling of π-allyl intermediates **C** are achieved by using aryl 1,3-dienes.[8i] Therefore, both electron-rich and electron-deficient aryl-substituted dienes were evaluated, yielding the corresponding three-component coupling products in good to excellent yields with >95:5 selectivity for the 1,2-addition product. A variety of vinyl triflates in combination with aryl boronic acid derivatives with common functional groups were evaluated. The use of simple cyclic vinyl triflates with different ring sizes (**4a**, **d**, **f**, **g**, **l**) led to excellent yields. Heterocyclic vinyl triflates (**4b**, **h**, **i**) also provide the corresponding products in modest to excellent yields. An acyclic vinyl triflate (**4j**) gave the desired product in moderate yield. Using a vinyl triflate derived from (+)-camphor produces **4k** in high yield but unfortunately a nearly 1:1 mixture of diastereomers. Various aryl boronic acids were also explored, wherein electronically disparate substituents or *ortho*-substitution on the arene had little influence on the reaction outcome. Of note, aryltriflates are not effective coupling

Table 2. Scope of the Three-Component Coupling of Vinyl Triflates, Aryl Boronic Acids, and Conjugated Dienes[a]

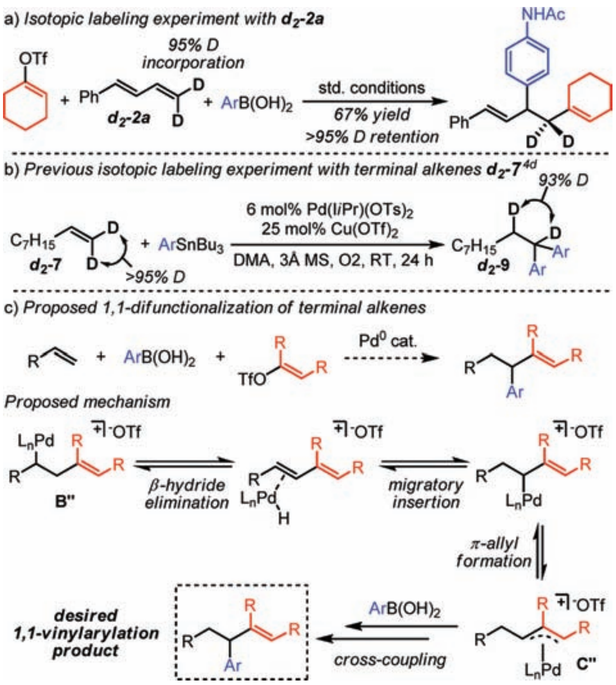


[a] Yields are average isolated yields of at least two experiments. In all cases the regioselectivity was >20:1 as determined by ^1H NMR spectroscopy. [b] An equimolar of diastereomers is observed.

partners and styrenes lead to a mixture of constitutional isomers under these reaction conditions.

The formation of a π-allyl-Pd-species similar to $\mathbf{C}'$ is a key proposal in this process as depicted in Scheme 1c. To probe if a species of this type is undergoing β-hydride elimination during the reaction, deuterated substrate **d_2-2a** was synthesized and subjected to the standard reaction conditions. No deuterium migration occurs during the course of the reaction as determined by ^{1}H NMR, ruling out the occurrence of β-hydride elimination of the π-allyl-Pd (Scheme 2a). This suggests as hypothesized above that π-allyl-Pd formation controls the outcome of the reaction, which is in good agreement with our previous observation in the 1,1-oxidative diarylation of terminal olefins with organostannanes that a deuterium label migrates in order to form a stabilized π-benzyl-Pd intermediate (Scheme 2b).[4c,d] The combination of these experiments suggests that the use of a terminal olefin in the current three-component coupling protocol should yield the 1,1-alkene difunctionalization product. Mechanistically, Heck insertion of a terminal olefin after oxidative addition of a vinyl triflate would yield unstabilized Pd-alkyl intermediate $\mathbf{B}''$. Selective β-hydride elimination at the allylic site and reinsertion of the Pd-hydride result in the formation of π-allyl-Pd intermediate $\mathbf{C}''$. Subsequent transmetalation of a boronic acid and reductive elimination produce the desired three-component coupling product. The use of simple terminal alkenes in three-component coupling chemistry of this sort has not been reported to the best of our knowledge.

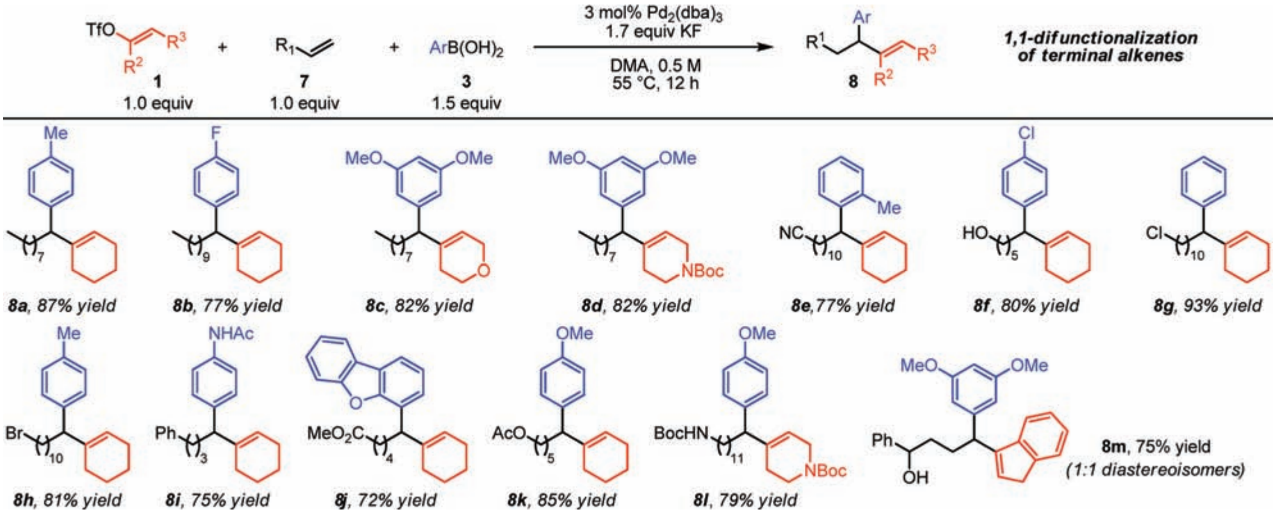
Scheme 2. Mechanistic Analysis



With no change to the optimized reaction conditions, the three-component coupling of terminal alkenes leads to generally excellent selectivity and yields for the desired 1,1-alkene difunctionalization product (Table 3). Olefins bearing common functional groups such as a nitrile (**8e**), a primary alkyl chloride (**8g**), esters (**8j**, **k**), a protected amine (**8l**), a free primary alcohol (**8f**), and a primary bromide (**8h**) were found to be compatible under these reaction conditions. Unfortunately, unprotected carboxylic acids and basic amines did not successfully undergo the three-component coupling. A variety of arylboronic acids proved to be effective coupling partners, providing high yields regardless of their electronic nature. A homoallylic alcohol cleanly undergoes coupling, although a 1:1 mixture of diastereomers results (**8m**). As noted above, heterocyclic vinyl triflates are excellent partners in this reaction (**8c**, **d**, **l**). In contrast to conjugated dienes, a limitation of this method is a general requirement of six-membered cyclic vinyl triflates to achieve selective formation of the endocyclic double bond (five- and seven-membered ring vinyl triflates yield a mixture of constitutional isomers). As an example, coupling with an acyclic vinyl triflate produced a 1:1 mixture of two regioisomers **8n** and **8n′**(see Supporting Information). These results further indicate the formation of a π-allyl-Pd intermediate like $\mathbf{C}''$. Presumably, in the case of six-membered vinyl triflates, the thermodynamically more favorable endocyclic double bond is formed. Control of constitutional isomer formation should considerably expand the utility of this process and is under current investigation.

In summary, we have combined the Suzuki reaction and the Heck reaction in an intermolecular fashion to achieve the

Table 3. Scope of the Three-Component Coupling of Vinyl Triflates, Aryl Boronic Acids, and Terminal Alkenes[a]



[a] Yields are average isolated yields of at least two experiments. In all cases the regioselectivity was >20:1 as determined by ^{1}H NMR spectroscopy.

difunctionalization of 1,3-dienes and terminal alkenes. The conditions are quite simple using reagents that are readily accessed and are not required in extreme excess. The scope of this reaction is relatively broad in terms of functional group compatibility and the products formed would be difficult to prepare rapidly using current methods. The success of this reaction class is attributed to the formation of stabilized, cationic π-allyl-Pd intermediates. In the case of conjugated dienes, the π-allyl-Pd intermediate is formed initially from Heck insertion of the alkene, which is faster than Suzuki cross-coupling under the optimized reaction conditions. In contrast, terminal alkenes undergo π-allyl-Pd formation by a proposed β-hydride elimination/Pd-hydride reinsertion rearrangement. The ability to form sp^2−sp^3 carbon−carbon bonds on the alkene framework with *different* coupling partners holds significant promise for synthetic endeavors. Future work is focused on probing the synthetic applications of this reaction class by developing enantioselective variants, evaluating broad classes of coupling partners, and understanding the underlying mechanistic features.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Experimental procedures and characterization data for new substances. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For reviews of the Heck reaction, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Coeffard, V.; Guiry, P. J. *Curr. Org. Chem.* **2010**, *14*, 212. (c) Narayanan, R. *Molecules* **2010**, *15*, 2124. (d) Anon *Chemtracts* **2010**, *23*, 61.

(2) (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (b) Feringa, B. L. *Transition Met. Org. Synth.* **1998**, *2*, 307. (c) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903.(d) Anderson, B. J.; Keith, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* 2010, *132*, 11872 and references therein.

(3) For a review, see: Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083.

(4) (a) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471. (b) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (c) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett.* **2010**, *12*, 2848. (d) Urkalan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146. (e) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076. (f) Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460.

(5) For examples of Pd-catalyzed alkene difunctionalization reactions under oxidative conditions, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181. (c) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962. (d) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846–3847. (e) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856. (f) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 8419.

(6) For an example of palladium-catalyzed diarylation of a vinyl ether, see: Trejos, A.; Fardost, A.; Yahiaoui, S.; Larhed, M. *Chem. Commun.* **2009**, 7587–7589.

(7) For diarylation of activated alkenes, see: Delample, M.; Villandier, N.; Douliez, J.-P.; Camy, S.; Condoret, J.-S.; Pouilloux, Y.; Barrault, J.; Jerome, F. *Green Chem.* **2010**, *12*, 804 and references cited therein.

(8) For examples of the formation of π-allyl-Pd intermediates by nucleophilic addition to a diene, see: (a) Bäckvall, J. E.; Nystroem, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676. (b) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308. (c) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (d) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. (e) Mino, T.; Kajiwara, K.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 2711. (f) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 16382. (g) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523. (h) Zhang, X.; Larock, R. C. *Tetrahedron* **2010**, *66*, 4265. (i) Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 10209. (j) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

(9) For the use of π-benzyl-Pd intermediates, see: (a) Becker, Y.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 845. (b) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166. (c) Lindsell, W. E.; Palmer, D. D.; Preston, P. N.; Rosair, G. M.; Jones, R. V. H.; Whitton, A. J. *Organometallics* **2005**, *24*, 1119. (d) Johns, A. M.; Tye, J. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 16010. (e) Narahashi, H.; Isao, S.; Yamamoto, A. *J. Organomet. Chem.* **2008**, *693*, 283. (f) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 9280. (g) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104.

(10) (a) Jutand, A.; Négri, S. *Organometallics* **2003**, *22*, 4229. (b) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810.

(11) For skipped diene synthesis, see: (a) Braddock, D. C.; Badine, D. M.; Gottschalk, T. *Synlett* **2001**, 1909. (b) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317. (c) Nájera, C. *J. Org. Chem.* **2009**, *74*, 2321.

(12) (a) Torii, S.; Okumoto, H.; Ozaki, H.; Nakayasu, S.; Kotani, T. *Tetrahedron Lett.* **1990**, *31*, 5319. (b) Torii, S.; Okumoto, H.; Kotani, T.; Nakayasu, S.; Ozaki, H. *Tetrahedron Lett.* **1992**, *33*, 3503. (c) Shaulis, K. M.; Hoskin, B. L.; Townsend, J. R.; Goodson, F. E.; Incarvito, C. D.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 5860.

(13) (a) Oh, C. H.; Lim, Y. M. *Tetrahedron Lett.* **2003**, *44*, 267. (b) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765. (c) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921. (d) Cheng, Y.-n.; Duan, Z.; Yu, L.; Li, Z.; Zhu, Y.; Wu, Y. *Org. Lett.* **2008**, *10*, 901. (e) Zhang, X.; Larock, R. C. *Tetrahedron* **2010**, *66*, 4265.

(14) (a) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677. (b) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590.

(15) (a) Huang, T.-H.; Chang, H.-M.; Wu, M.-Y.; Cheng, C.-H. *J. Org. Chem.* **2001**, *67*, 99. (b) Aftab, T.; Grigg, R.; Ladlow, M.; Sridharan, V.; Thornton-Pett, M. *Chem. Commun.* **2002**, 1754. (c) Shu, W.; Jia, G.; Ma, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 2788.

(16) For three-component couplings of this type with 1,3-dienes using other metals, see: (a) Mizutani, K.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2003**, *5*, 3959. (b) Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. *Adv. Synth. Catal.* **2004**, *346*, 905.

(17) (a) Wayland, B. B.; Schramm, R. F. *Inorg. Chem.* **1969**, *8*, 971. (b) Bueno, A. C.; de, S. A. O.; Gusevskaya, E. V. *Adv. Synth. Catal.* **2009**, *351*, 2491.