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Palladium-Catalyzed γ-Selective and Stereospecific Allyl−Aryl Coupling between Acyclic Allylic Esters and Arylboronic Acids

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Abstract: Reactions between acyclic (*E*)-allylic acetates and arylboronic acids in the presence of a palladium catalyst prepared from $Pd(OAc)_2$, phenanthroline (or bipyridine), and $AgSbF_6$ (1:1.2:1) proceeded with excellent γ-selectivity to afford allyl−aryl coupling products with *E*-configuration. The reactions of α-chiral allylic acetates took place with excellent α-to-γ chirality transfer with *syn* stereochemistry to give allylated arenes with a stereogenic center at the benzylic position. The reaction tolerated a broad range of functional groups in both the allylic acetates and the arylboronic acids. Furthermore, γ-arylation of cinnamyl alcohol derivatives afforded *gem*-diarylalkane derivatives containing an unconjugated alkenic substituent. The synthetic utility of this method was demonstrated by its utilization in an efficient synthesis of (+)-sertraline, an antidepressant agent. The observed γ-regioselectivity and *E*-1,3-*syn* stereochemistry were rationalized based on a Pd(II) mechanism involving transmetalation between a cationic mono(acyloxo)palladium(II) complex and arylboronic acid, and directed carbopalladation followed by *syn*-β-acyloxy elimination. The results of stoichiometric reactions of palladium complexes related to possible intermediates were fully consistent with the proposed mechanism.

Introduction

Transition-metal-catalyzed allylic substitution reactions with carbon nucleophiles are among the most important carbon−carbon bond formation methods in modern organic synthesis because of their broad substrate scope under mild reaction conditions and applicability to enantioselective reactions, as well as the versatility of the alkene functionality adjacent to the chiral center for stereoselective derivatization. For example, Tsuji−Trost allylic substitution involving a (π-allyl)metal intermediate has made impressive progress in this regard.[1] However, allylic substitution of unsymmetrically substituted allylic substrates occurs competitively at the α- and γ-positions due to formation of a (π-allyl)metal intermediate (Scheme 1a): the regioselectivity is highly dependent on the substitution pattern of the allylic substrates. Therefore, most previous studies in this area have focused on cases in which an allylic system is located at a terminal of a molecule or is highly asymmetrized by electronic and/or steric substituent effects.

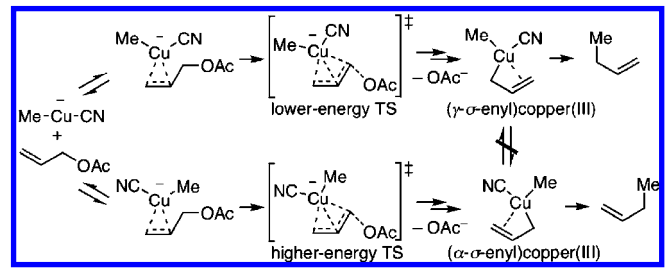
One way to address the issue of the regiochemical control in allylic substitution is to employ strongly nucleophilic, mostly ate-type, organometallic reagents ($R-M^-$) such as monoalkyl heterocuprate reagents ($[R-Cu-X]^-$).[2,3] Allylic substitution reactions of this type show characteristic γ-regioselectivity (Scheme 1b). The reaction of α-chiral allylic compounds allows for the construction of a new stereogenic carbon center at the γ-position through 1,3-chirality transfer. The γ-selectivity has often been explained based on a hypothetical reaction pathway as shown in Scheme 1b: formal S_N2' attack of the organometallic nucleophile ($R-M^-$) produces a (σ-allyl)metal species (oxidative addition), and reductive elimination results in C−C bond formation at the γ-position.[4] Although these processes proceed with excellent γ-selectivity in many cases, the γ-substitution

(1) (a) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144–152. (b) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615–2649. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943.

(2) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002.

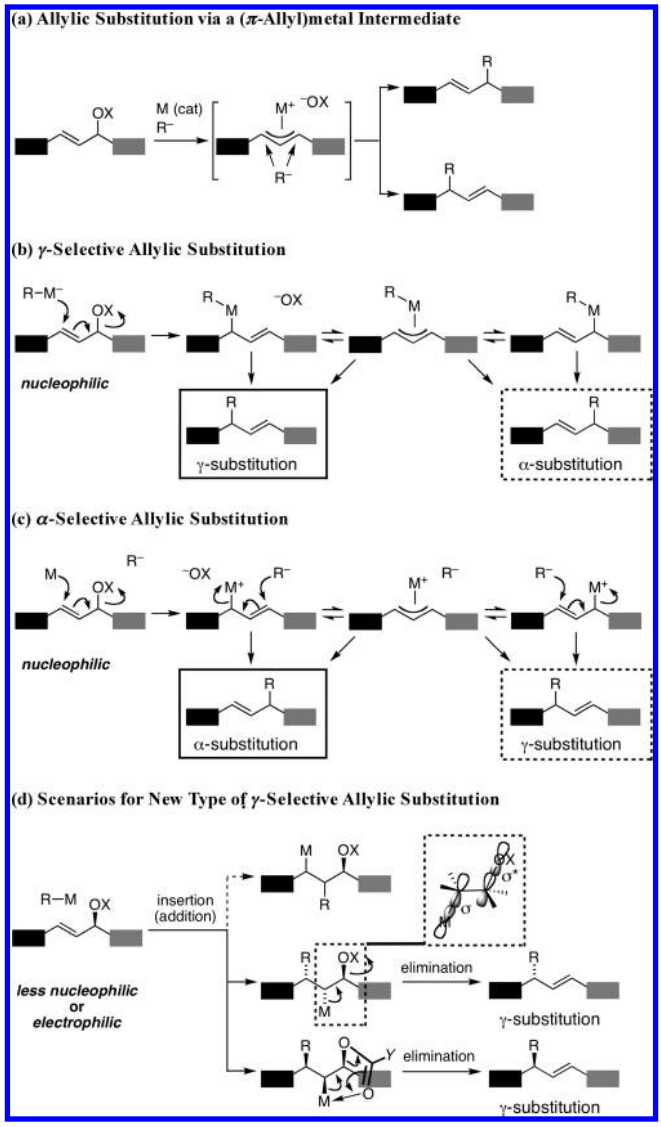
(3) Even for Cu-catalyzed systems, studies to date have focused largely on the reactions of primary allylic electrophiles that give terminal alkenes. For reviews of enantioselective allylic substitutions catalyzed by chiral copper complexes, see: (a) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435–4439. (b) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765–3780.

(4) According to DFT studies by Nakamura *et al.*, the reaction of monoalkyl cyanocuprate MeCu(CN)Li with allyl acetate forms a (γ-σ-enyl)copper(III) species (enyl[$\sigma+\pi$] complex) rather than a γ-σ-allylcopper(III) species as shown in Scheme 1b. The (γ-σ-enyl)copper(III) species does not adopt an equilibrium with the corresponding (α-σ-enyl)coppor(III) species. Regioselectivity is determined at the oxidative addition step as a consequence of the asymmetric nature of $MeCuCN^-$. See: (a) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862–12863. (b) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287–6293.



10.1021/ja9092264

Scheme 1. Metal-Mediated Allylic Substituions



product is in some cases contaminated with a small but significant amount of the corresponding α-isomer, while in other cases regioselectivity is almost lost.[5,6] According to the hypothetical mechanism shown in Scheme 1b, the α-isomer is formed through $\sigma-\pi-\sigma$ isomerization of the allylmetal intermediates.

While rather rare, α-selective allylic substitutions mediated by transition metal complexes have also been reported. For example, certain low-valent rhodium, ruthenium, and iron complexes preferentially deliver α-substitution products in reactions between allylic carbonates and soft carbon nucleophiles such as malonate anions (Scheme 1c).[7−9] The reactions of α-chiral allylic compounds generally proceed with retention of configuration. A mechanistic hypothesis to explain this regioselectivity is summarized in Scheme 1c: strongly nucleophilic (low-valent) transition metal complexes (M) attack the allylic substrates in an S_N2' manner to form (σ-allyl)metal complexes, which undergo a second S_N2' displacement with a carbon nucleophile (R^-). As with γ-selective substitution using organometallic reagents ($R-M^-$) (Scheme 1b), however, the regioselectivity of these α-substitution reactions is not always complete.[7,9] As shown in Scheme 1c, concomitant γ-substitution proceeds through $\sigma-\pi-\sigma$ allylic isomerization, which occurs before the attack of the carbon nucleophile (R^-).

In order to develop an alternative to existing regioselective allylic substitutions, we contrived new γ-selective strategies based on reaction pathways that proceed without forming the problematic allylmetal species (Scheme 1d). We assumed that an organometallic species (R−M) that is less nucleophilic than M and $R-M^-$ in Scheme 1a−c would undergo carbometalation across the C−C double bond (insertion) rather than oxidative addition to form an allylmetal species with a higher metal oxidation state. Regioselectivity in the carbometalation reaction would be induced either by stereoelectronic effects that stabilize the σ ($C_\beta-M$) orbital through interactions with the σ^* ($C_\alpha-OX$) orbital or with the assistance of intramolecular coordination by the leaving group (OX). β-Elimination of M−OX from the alkylmetal intermediate would afford a formal S_N2' product.[10] Furthermore, we knew that electrophilic or less nucleophilic organometallic species could be prepared by a well established transmetalation reaction between an acetoxopalladium(II) complex and organoboronic acids.[11]

(5) The reaction of MeCu(CN)Li and *cis*-1-D-5-methyl-2-cyclohexenyl acetate, which is a regiochemically unbiased substrate, showed 96:4 γ/α-selectivity: See ref 26b. For selected papers on γ-selective and stereoselective allylic substitution reactions with stoichiometric alkylcopper(I) reagents with excellent 1,3-chirality transfer, see: (a) Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130–1136. (b) Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055–4061. (c) Breit, B.; Demel, P.; Studte, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3786–3789. (d) Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627–4631.

(6) When either arylcopper reagents or cinnamyl alcohol derivatives were employed, the γ-selectivity is considerably reduced. See: refs 5c and 29. For allylic substitution reactions with stoichiometric arylcopper(I) reagents with excellent γ-selectivity, see: (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114. (b) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722. (c) Recently, Tomioka *et al*. reported the highly γ-selective, enantioselective substitution of cinnamyl bromides with aryl Grignard reagents. See: Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733–8735.

(7) For Rh-catalyzed α-selective allylic substitutions with carbon nucleophiles, see: (a) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *39*, 1725–1728. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581–5582. (c) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974–8975. (d) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 8642–8643. (e) Evans, P. A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, *125*, 7158–7159. (f) Ashfeld, B. L.; Miller, K. A.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1321–1324. The stereospecificity of the Rh catalysis has been explained based on the [$\sigma+\pi$] nature of the allyl (enyl) ligand.

(8) For Ru-catalyzed α-selective allylic substitution with soft carbon nucleophiles, see: Kawatsura, M.; Ata, F.; Hayase, S.; Itoh, T. *Chem. Commun.* **2007**, 4283–4285.

(9) For Fe-catalyzed α-selective allylic substitutions with soft carbon nucleophiles, see: (a) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 513–514. (b) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469–1473. (c) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 6053–6056.

(10) For studies in this line [Cu-catalyzed γ-selective allylic and propargylic substitutions with bis(pinacolato)diboron], see: (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857. (c) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7424–7427. (d) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774–15775.

(11) For a mechanistic study of the formation of a (σ-aryl)palladium(II) intermediate by transmetalation with arylboronic acid and $Pd(OAc)_2$, see:Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351.

Table 1. Palladium-Catalyzed Coupling between **1a** and **2a** under Various Conditions[a]

entry	Pd	silver salt (mol %)	solvent	conv. (%)	NMR yield of **3a** (%)[b,d]
1	$Pd(OAc)_2$	none	DCE	70	54
2	$Pd(OAc)_2$	$AgSbF_6$ (10)	DCE	91	84 (80)[c]
3	$Pd(OAc)_2$	$AgSbF_6$ (20)	DCE	100	15
4	$Pd(OAc)_2$	$AgBF_4$ (10)	DCE	100	81
5	$Pd(OAc)_2$	AgOTf (10)	DCE	100	68
6	$Pd(OAc)_2$	$AgNTf_2$ (10)	DCE	100	70
7	$Pd(OAc)_2$	$AgPF_6$ (10)	DCE	100	48
8	$Pd(OAc)_2$	$AgSbF_6$ (10)	THF	58	58
9	$Pd(OAc)_2$	$AgSbF_6$ (10)	DME	52	52
10	$Pd(OAc)_2$	$AgSbF_6$ (10)	acetone	88	51
11	$Pd(OAc)_2$	$AgSbF_6$ (10)	MeOH	34	20
12	$Pd(OAc)_2$	$AgSbF_6$ (10)	DMA	37	15
13	$Pd(OAc)_2$	$AgSbF_6$ (10)	toluene	16	13
14	$Pd(OAc)_2$	$AgSbF_6$ (10)	CPME	29	29
15	$Pd(OAc)_2$	$AgSbF_6$ (10)	dioxane	70	29
16	$Pd(OCOCF_3)_2$	$AgSbF_6$ (10)	DCE	80	40
17	$PdCl_2$	$AgSbF_6$ (10)	DCE	100	<5
18	$PdCl_2(CH_3CN)_2$	$AgSbF_6$ (10)	DCE	100	<5
19	$[Pd(dppe)(PhCN)_2](SbF_6)_2$	−	DCE	0	0

[a] Conditions: Pd (10 mol %), 1,10-phenanthroline (12 mol %), Ag (0−20 mol %), **1a** (0.25 mmol), phenylboronic acid (**2a**) (0.375 mmol), solvent (1.0 mL), 60 °C, 12 h. [b] Determined by ^{1}H NMR. [c] The yield in parentheses was isolated yield. [d] Isomeric ratios (γ/α > 99:1, *E*/*Z* > 20:1). Determined by ^{1}H NMR.

Our studies based on the aforementioned scenarios led to the development of a new allylic substitution methodology that allows for palladium-catalyzed coupling between acyclic (*E*)-allylic esters and arylboronic acids, which proceeds with excellent γ-*E*-selectivity and with excellent 1,3-*syn*-chirality transfer.[12−17] This reaction tolerated a variety of functional groups in both acyclic (*E*)-allylic acetates and arylboronic acids and is even applicable to allylic systems that are conjugated with an aromatic π-system. It should be noted that the palladium-catalyzed methodology enables the use of sp^2-carbon nucleophiles such as arylmetal reagents, which have not been well exploited in copper chemistry due to their poor nucleophilicity.[18]

Results and Discussion

Optimization of Palladium-Catalyzed Allyl−Aryl Coupling Reaction. In order to focus on issues of regioselectivity in the initial studies, we selected the unsymmetrically substituted allylic acetate **1a** as a substrate. This has similar steric bulk at the α- and γ-positions, which was expected to lead to low regioselectivity in terms of (π-allyl)metal chemistry (Table 1). First, we examined the reaction between **1a** and phenylboronic acid (**2a**) (1.5 equiv) in the presence of $Pd(OAc)_2$ (10 mol %) and 1,10-phenanthroline (12 mol %) in 1,2-dichloroethane (DCE). Gratifyingly, the reaction at 60 °C for 6 h afforded the allyl−aryl coupling product **3a** in 54% NMR yield (70% conv. of **1a**) with excellent regio- (**3a**/**3f** >99:1) and *E*/*Z*- (>20:1) selectivity (entry 1, see Table 2, entry 11 for the structure of **3f**).[19]

The addition of a catalytic amount of silver salt improved the yield of **3a** significantly. The reaction with $AgSbF_6$ additive (10 mol %, Pd/Ag 1:1) afforded **3a** in 80% isolated yield (91% conv. of **1a**) with regio- and *E*-selectivity unchanged (Scheme 2 and Table 1, entry 2). Increasing the amount of $AgSbF_6$ from 10 to 20 mol %, however, caused considerable side reactions and resulted in a drastic decrease in the yield of **3a** (15% by NMR, 100% conv., entry 3). Several other silver salts were also examined (entries 4−7). While $AgBF_4$ was as effective as $AgSbF_6$, giving **3a** in 81% yield (entry 4), the use of AgOTf, $AgNTf_2$, and $AgPF_6$ resulted in lower reaction efficiency (entries 5−7).

(12) Part of this work was communicated. See: Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277.

(13) Pd-catalyzed γ-selective allyl−aryl coupling between aryl iodides and allylic acetates has been reported. However, the reaction required harsh conditions (typically 180 °C) and was not stereoselective. See: (a) Mariamphillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745–4747.

(14) Maddaford et al. reported the palladium-catalyzed *C*-glycosidation of peracetylated glycals (γ-substitution of γ-alkoxy-substituted allylic acetates with *anti*-stereochemistry) with arylboronic acids. This reaction goes through a (π-allyl)palladium(II) intermediate. Regioselectivity is controlled by the electronic effect of the oxygen functionality and is limited to this specific substrate class. See:Ramanauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013–2015.

(15) For palladium-catalyzed allyl-sp^2-carbon couplings between allyl alcohol derivatives and organoboron compounds via a (π-allyl)palladium(II) intermediate, see: (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980. (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1990**, *31*, 7453–7456. (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384–3388. (d) Kabalka, G. W.; Al-Masum, M. *Org. Lett.* **2006**, *8*, 11–13. (e) Mino, T.; Kajiwara, K.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 2711–2715. (f) Nishikata, T.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 12103–12105. See also ref 14.

(16) For rhodium-catalyzed allyl-aryl couplings between *cis*-4-cyclopenten-1,3-diol derivatives and arylboron compounds that afforded *trans*-2-aryl-3-cyclopenten-1-ol derivatives, see: (a) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569–4572. (b) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595–597.

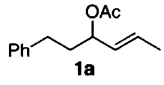
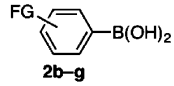
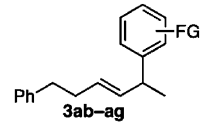
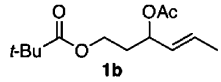
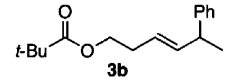
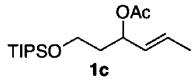
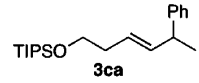
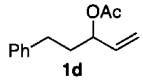
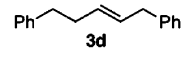
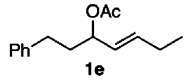
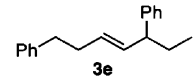
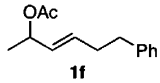
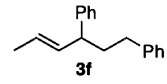
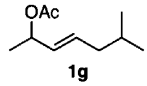
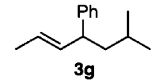
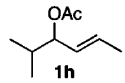
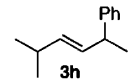
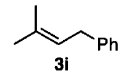
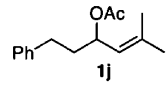
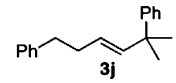
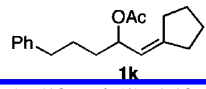
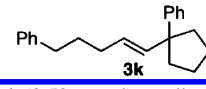
(17) For palladium-catalyzed oxidative Mizoroki−Heck-type reactions of allylic acetates with arylboronic acids, see: (a) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076–15077. (b) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424–2425. (c) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980–2983.

(18) For γ-selective allylic substitution reactions with stoichiometric arylcopper(I) reagents with excellent 1,3-chirality transfer, see: refs 6a and 6b.

(19) The γ/α selectivity (>99:1) was unambiguously determined by the ^{1}H NMR and GC analysis of the crude product, using the corresponding α-isomer (**3f**) as a reference compound.

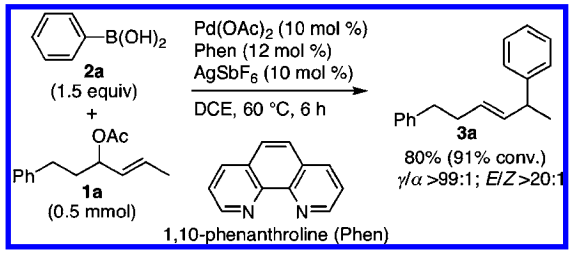
(20) (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768–2770. (b) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807–817. (c) Davis, J. A.; Hartley, F. R.; Muray, S. G. *J. Chem. Soc., Dalton Trans.* **1980**, 2246–2249.

Table 2. Palladium-Catalyzed Reaction of Allylic Acetates with Arylboronic Acids[a]

entry	allylic acetate	boronic acid	product[b]	yield[c] (%)
1[d,e]	 **1a**	 **2b–g** FG = 4-OMe (**2b**)	 **3ab–ag** **3ab**	41
2		FG = 4-CF_3 (**2c**)	**3ac**	82
3		FG = 4-Cl (**2d**)	**3ad**	80
4		FG = 4-COMe (**2e**)	**3ae**	81
5[e]			**3af**	71
6[d,e]		FG = 3-CHO (**2f**)	**3ag**	43
		FG = 2-Me (**2g**)		
7	 **1b**	$PhB(OH)_2$ (**2a**)	 **3b**	72
8	 **1c**	$PhB(OH)_2$ (**2a**)	 **3ca**	68
9[g]	 **1d**	$PhB(OH)_2$ (**2a**)	 **3d**	84
10	 **1e**	$PhB(OH)_2$ (**2a**)	 **3e**	70
11[e,f]	 **1f**	$PhB(OH)_2$ (**2a**)	 **3f**	48
12[e]	 **1g**	$PhB(OH)_2$ (**2a**)	 **3g**	39
13	 **1h**	$PhB(OH)_2$ (**2a**)	 **3h**	76
14[g]	 **1i**	$PhB(OH)_2$ (**2a**)	 **3i**	75
15	 **1j**	$PhB(OH)_2$ (**2a**)	 **3j**	62
16[e,h]	 **1k**	$PhB(OH)_2$ (**2a**)	 **3k**	41

[a] Conditions: $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (12 mol %), $AgSbF_6$ (10 mol %), **1** (0.50 mmol), arylboronic acid (**2**) (0.75 mmol), DCE (3.0 mL), 60 °C, 12 h. [b] Isomeric ratios (γ/α > 20:1, *E*/*Z* > 20:1). Determined by ^1H NMR. See ref 22. [c] Isolated yield. [d] Conditions: $Pd(OAc)_2$ (10 mol %), 2,2′-bipyridine (12 mol %), $AgSbF_6$ (10 mol %), **1** (0.50 mmol), arylboronic acid (**2**) (0.75 mmol), DME (3.0 mL), 60 °C, 12 h. [e] Unreacted allylic acetate (**1**) was detected in the crude material by ^1H NMR analysis (entry 1, 29%; entry 5, 14%; entry 6, 41%; entry 11, 32%; entry 12, 15%; entry 16, 30%). [f] Isomeric ratios [γ/α (**3f**/**3a**) > 99:1, *E*/*Z* > 20:1]. See ref 19. [g] Conditions: $Pd(OAc)_2$ (5 mol %), 1,10-phenanthroline (10 mol %), $AgSbF_6$ (10 mol %), **1i** (0.50 mmol), $PhB(OH)_2$ (**2a**) (0.75 mmol), THF (3.0 mL), 60 °C, 12 h. [h] Conditions: $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (12 mol %), $AgSbF_6$ (10 mol %), **1k** (0.25 mmol), $PhB(OH)_2$ (**2a**) (0.375 mmol), DCE (1.5 mL), 60 °C, 12 h.

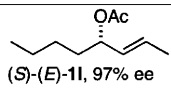
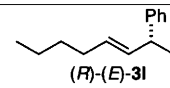
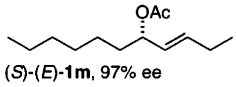
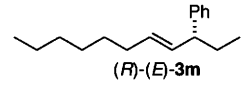
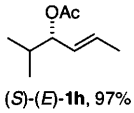
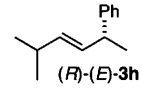
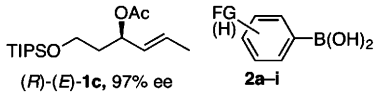
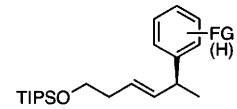
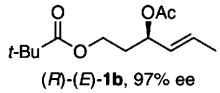
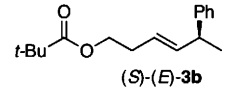
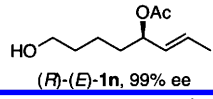
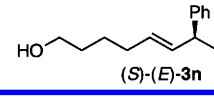
Scheme 2. γ-Selective Coupling between **1a** and **2a**



Screening of solvents for the reaction of **1a** identified 1,2-dichloroethane (DCE) as the optimum solvent, affording **3a** in 84% yield (Table 1, entries 2, 8−15). Ethereal solvents such as THF and 1,2-dimethoxyethane (DME) were also useful, although the conversion to **3a** was slightly decreased (entries 8 and 9). However, the reactions in acetone and 1,4-dioxane produced small amounts of conjugated dienes stemming from the elimination reaction of the allylic acetate alone as side products (entries 10 and 15). The use of MeOH, *N*,*N*′-dimethylacetamide (DMA), toluene, and cyclopentyl methyl ether (CPME) resulted in significantly lower yields of **3a** (entries 11−14).

The use of $Pd(OAc)_2$ as a source of palladium was essential for the promotion and regioselectivity of allyl−aryl coupling (Table 1, entries 16−18). When $Pd(OCOCF_3)_2$ was employed instead of $Pd(OAc)_2$, the product was obtained in low yield with poor regioselectivity (γ/α 78:22, entry 16). Catalysts prepared from $PdCl_2$ and $PdCl_2(CH_3CN)_2$ were useless for the coupling

Table 3. 1,3-Chirality Transfer[a]

entry	allylic acetate	boronic acid	product		yield[b,c] (%)	ee (%) of **3**
1[d]	 (*S*)-(*E*)-**1l**, 97% ee	$PhB(OH)_2$ (**2a**)	 (*R*)-(*E*)-**3l**		65	97
2	 (*S*)-(*E*)-**1m**, 97% ee	$PhB(OH)_2$ (**2a**)	 (*R*)-(*E*)-**3m**		62	95
3[d]	 (*S*)-(*E*)-**1h**, 97% ee	$PhB(OH)_2$ (**2a**)	 (*R*)-(*E*)-**3h**		58	97
4	 (*R*)-(*E*)-**1c**, 97% ee **2a–i**	FG = H (**2a**)	 (*S*)-(*E*)-**3ca–ci**	**3ca**	75	97
5		FG = 4-OMe (**2b**)		**3cb**	56	97
6		FG = 4-Cl (**2d**)		**3cd**	81	95
7		FG = 4-COMe (**2e**)		**3ce**	71	97
8[e]				**3cf**	67	87
9		FG = 3-CHO (**2f**)		**3ch**	66	95
10		FG = 4-CHO (**2h**)		**3ci**	69	94
		FG = 3-CF_3 (**2i**)				
11	 (*R*)-(*E*)-**1b**, 97% ee	$PhB(OH)_2$ (**2a**)	 (*S*)-(*E*)-**3b**		66	97
12	 (*R*)-(*E*)-**1n**, 99% ee	$PhB(OH)_2$ (**2a**)	 (*S*)-(*E*)-**3n**		63	98

[a] Conditions: $Pd(OAc)_2$ (10 mol %), 2,2′-bipyridine (12 mol %), $AgSbF_6$ (10 mol %), **1** (0.25 mmol), arylboronic acid (**2**) (0.375 mmol), DME (1.5 mL), 60 °C, 12 h. [b] Isolated yield. [c] Isomeric ratios (γ/α > 20:1, *E*/*Z* > 20:1). Determined by ^1H NMR. See ref 22. [d] Conditions: $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (12 mol %), $AgSbF_6$ (10 mol %), **1** (0.25 mmol), arylboronic acid (**2**) (0.375 mmol), DCE (1.5 mL), 60 °C, 12 h. [e] NMR yield.

reaction, producing complex mixtures (entries 17 and 18). The dicationic palladium complex $[Pd(dppe)(PhCN)_2](SbF_6)_2$[20] was totally inactive (entry 19).

Ligand screening for the reaction of **1a** or **1l** (see Table 3 for the structure of **1l**) revealed that 1,10-phenanthroline and 2,2′-bipyridine were equally the most effective and that the use of a ligand with a partial bisimine structure (−N═C(R)−C(R)═N−) was essential for the efficiency of the catalytic system. Another conclusion of the screening was that the reaction was highly sensitive to the steric demands of ligands. 2,2′-Bipyridyl was as effective as 1,10-phenanthroline (84% yield). The electronic effect of the substituent on the aromatic ring of phenanthroline or bipyridine did not result in an improvement in catalytic activity. A more hindered phenanthroline such as neocuproine blocked the reaction completely. The $N(sp^3)$-ligand TMEDA was much less effective (17% yield), and no reaction occurred when (−)-sparteine was used. Phosphine ligands such as PPh_3, PBu_3, and DPPE inhibited the allyl−aryl cross-coupling reaction completely, giving only a trace of biphenyl. The reaction without 1,10-phenanthroline afforded a complex mixture with no allyl−aryl coupling product (100% conv.).

Overall, our studies led to the conclusion that the optimum conditions for selective conversion of **1a** and **2a** (1.5 equiv) to **3a** were 10 mol % $Pd(OAc)_2$, 12 mol % 1,10-phenanthroline, and 10 mol % $AgSbF_6$ in DCE at 60 °C (Scheme 2 and Table 1, entry 2).[21] Notably, the palladium-catalyzed allylic substitution reaction could be performed under air and in undried solvent without affecting the product yield and selectivity.

Substrate Scope. When palladium-catalyzed allyl−aryl coupling was applied to various combinations of allylic acetates (**1**) and arylboronic acids (**2**) (Table 2), the reactions afforded the γ-substitution products **3** exclusively, irrespective of the substitution pattern of the allylic acetate.[22,23] Moreover, the reactions took place with excellent *E*-selectivity (not applicable to **1i**, entry 14). The reaction tolerated a variety of functional groups in both **1** and **2**: MeO, CF_3, chloride, ketone, aldehyde, ester, and silyl ether functionalities can be present (entries 1−5 and 7, 8).

Table 2 also shows, however, that the efficiency of the reaction was sensitive to the steric demand of **2** and the γ-substituent of **1**, but substantial steric bulk was tolerated at the α-position. For instance, *o*-tolylboronic acid (**2g**) was less reactive than phenylboronic acid (**2a**) toward the reaction with **1a**, giving the coupling product (**3ag**) in only 43% isolated yield (entry 6). Furthermore, as the γ-substituent became bulkier (H < Me < Et < CH_2CH_2Ph < *i*-Bu), the product yield decreased

(21) Reducing the amount of phenylboronic acid (**2a**) decreased the yield of the coupling product **3a** under otherwise identical conditions.

(22) For Schemes 2 and 3 and Tables 2 and 3, the crude materials after removal of the catalyst and boron compounds consisted of the coupling product, biaryl, unreacted allylic acetate, and/or unidentified compounds. The Mizoroki−Heck-type product was not detected. The isolated products were contaminated with traces of unidentified materials (0.1−5%). The isolated yields for the reaction of **1g**,**h**,**i**,**l** in Tables 2 and 3 may be reduced by the evaporation of the products.

(23) The reaction of terminal alkenes **1d** and **1i** were carried out with THF solvent (Table 2, entries 9 and 14). The use of THF suppressed the formation of unidentified side products.

(Scheme 1 and Table 1, entries 9−12). On the other hand, allylic acetates **1h** and **1i**, bearing a bulky isopropyl group and two methyl groups, respectively, at the α-position were efficiently coupled with **2a** (entries 13 and 14).

Notably, the reaction of γ,γ-disubstituted allylic acetates such as **1j** and **1k** with phenylboronic acid (**2a**) occurred under identical conditions (10 mol % Pd, DCE, 60 °C, 6 h), delivering the phenyl group at the fully substituted γ-carbon atom (entries 15 and 16). Therefore, Pd-catalyzed allyl−aryl coupling represents a powerful tool for the construction of benzylic all-carbon quaternary centers.

Our attempt to use the pinacolato ester of phenylboronic acid as a coupling partner with **1a** resulted in no reaction. Furthermore, neither alkenylboronic acids nor their ester derivatives showed reactivity toward coupling with **1a**.

α-to-γ Chirality Transfer. Allyl−aryl coupling with optically active allylic acetates took place with excellent α-to-γ chirality transfer with *syn*-stereochemistry (Table 3).[22] In our previous work,[12] all reactions were performed in the presence of $Pd(OAc)_2$, 1,10-phenanthroline, and $AgSbF_6$ in 1,2-dichloroethane. After further investigation, a combination of $Pd(OAc)_2$, 2,2′-bipyridine, and $AgSbF_6$ in 1,2-dimethoxyethane was found to be suitable in terms of the efficiency of 1,3-chirality transfer. Under the previous conditions, (*S*)-(*E*)-**1m** (97% ee), bearing a γ-Et group, and (*R*)-(*E*)-**1c** (97% ee), bearing a silyl ether functionality, were transformed into (*R*)-(*E*)-**3m** (89% ee) and (*S*)-(*E*)-**3c** (92% ee), respectively, with significant reductions in enantiomeric purity. In contrast, reactions under the new conditions afforded (*R*)-(*E*)-**3m** (95% ee) and (*S*)-(*E*)-**3c** (97% ee) with high levels of chirality transfer (entries 2 and 4).

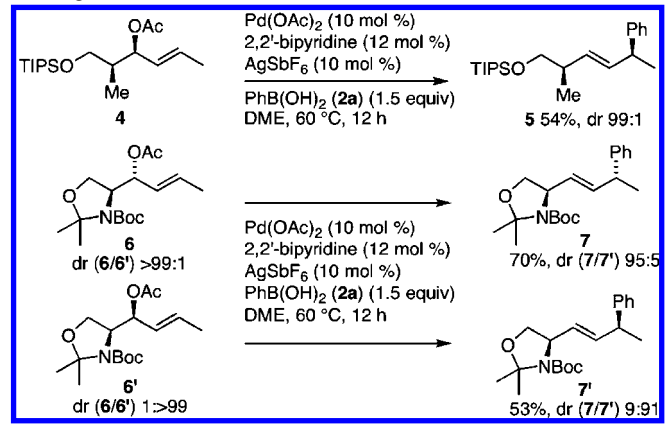
Notably, functionalities such as MeO, Cl, ketone, aldehyde, silyl ether, CF_3, and ester were tolerated in both the allylic acetates (**1**) and the arylboronic acids (**2**), giving the corresponding coupling product with excellent 1,3-chirality transfer (entries 4−12). More interestingly, even the allylic acetate (**1n**) with a nonprotected hydroxyl group underwent coupling with excellent chirality transfer (entry 12).

We also examined the effect of the substrate backbone on α-to-γ chirality transfer. The reaction of (*S*)-(*E*)-**1l** (97% ee), which has α-Bu and γ-Me substituents, with **2a** gave (*R*)-(*E*)-**3l** with 97% ee (entry 1, previous conditions). Under identical conditions, the reaction of (*S*)-(*E*)-**1h** (97% ee), which contains bulky α-*i*-Pr (instead of α-Bu in (*E*)-**1l**) and γ-Me substituents, gave (*R*)-(*E*)-**3h** with 97% ee (entry 3), suggesting that the chirality transfer is not significantly influenced by the steric demand of the α-substituent.

In sharp contrast to the results for allylic acetates with an *E*-configuration, the reaction of (*S*)-(*Z*)-**1l** (97% ee) gave (*S*)-(*E*)-**3l** with 77% ee in 36% isolated yield (71% conv.). Although the 1,3-*syn* stereochemistry was retained, selectivity was significantly decreased. The reaction of *cis*-4-cyclopentene-1,3-diol diacetate afforded the *trans*-1,2-isomer stereoselectively in only 19% yield. The low reactivity of the cyclic substrate and the unusual 1,3-*anti* stereochemistry may have been due to steric repulsion between the acetoxy group and an incoming phenylpalladium(II) species (*vide infra* for mechanistic discussion). These results allowed us to conclude that the utility of the present Pd-catalyzed allyl−aryl coupling protocol was limited to the reaction of acyclic allylic esters with an *E*-configuration.[24]

The palladium catalyst system was effective for diastereoselective reactions of the allylic substrates **4**, **6**, and **6′**, which have consecutive chiral centers (Scheme 3).[22] Allylic acetate **4** underwent highly stereoselective coupling to produce the optically pure allylated arene **5** in 54% yield (dr 99:1). The coupling reaction was also applicable to the diastereomers **6** and **6′**, which were prepared in three steps from Garner aldehyde, respectively. Both **6** and **6′** underwent diastereoselective coupling reactions to furnish optically active allylarenes **7** (**7**/**7′** 95:5) and **7′** (**7**/**7′** 9:91), respectively, leaving the amide moiety untouched.

Scheme 3. Diastereoselective Reactions of Allylic Substrates Having Consecutive Chiral Centers[a]



[a] Diasteromeric ratios were determined by ^1H NMR and GLC.

Synthesis of *gem*-Diarylalkanes. Chiral *gem*-diarylalkane structures are found in many important pharmaceuticals and bioactive natural compounds,[25] such as tolterodine, CDP-840, nomifensine, sertraline (**8**), podophyllotoxin, and etoposide. The construction of chiral *gem*-diarylalkane structures is key to the efficient synthesis of these pharmaceuticals. Given that the coupling of chiral cinnamyl esters with arylboronic acids occurs regioselectively at the benzylic γ-position in a stereospecific manner, this method was expected to be an excellent protocol for constructing *gem*-diarylalkanes. However, there were three possible challenges. First, delivery of the aryl group to the γ-position would result in breaking of the π-conjugation between the C−C double bond and the aromatic system in the starting materials. Second, the steric demand of the aromatic substituent at the γ-position might prevent the reaction. Third, "incorrect" regiochemistry in the aryl−Pd addition across the C−C double bond would result in the formation of stable σ- or π-benzylic palladium(II) species, which might undergo subsequent β-hydride elimination to form highly conjugated Mizoroki−Heck type products (stilbene derivatives).

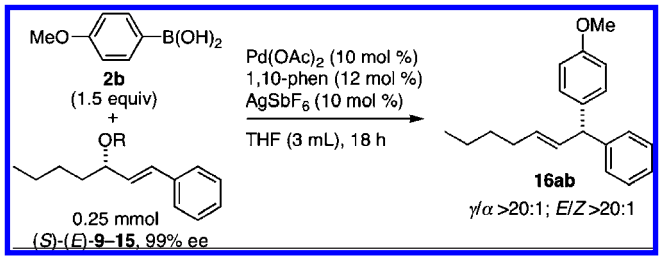
In fact, the literature indicates that γ-substitution of cinnamyl alcohol derivatives is difficult in the reactions of cuprate reagents (Scheme 1b). For instance, the reaction of (*E*)-α-methylcinnamyl acetate with lithium dialkyl cuprate (Me_2CuLi) proceeded in favor of the more thermodynamically stable α-substitution products with a selectivity of 95%.[26] Even with a monoalkyl heterocuprate, MeCu(CN)Li, which generally shows greater γ-selectivity, γ-selectivity was only

(24) Cyclic substrates showed low reactivities. For instance, the reaction of 1-acetoxy-2-cyclohexene with **2a** [$Pd(OAc)_2$, 10 mol %; 1,10-phenanthroline, 12 mol %; $AgSbF_6$,10 mol %; THF; 60 °C] afforded the corresponding coupling product in only 17% yield.

(25) See ref 6c and references therein.

(26) (a) Goering, H. L.; Seitz, E. P.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304–5308. (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422–426.

Table 4. Effect of Leaving Groups in the Pd-Catalyzed Coupling between Cinnamyl Esters (**9**−**15**) and **2b**



enrty	R (**9**−**15**)	temp (°C)	conv. (%)	isolated yield (%)[a]	ee (%)
1	CH_3CO (**9**)	60	68	60	96
2	CH_3CO (**9**)	40	38	35	98
3	C_6H_5CO (**10**)	40	47	43	97
4	2-MeO-C_6H_4CO (**11a**)	40	72	70	99
5	2-Me-C_6H_4CO (**12**)	40	63	58	98
6	2-CF_3−C_6H_4CO (**13**)	40	67	62	98
7	2,6-$(MeO)_2$-C_6H_4CO (**14**)	40	21	23	–
8	4-MeO-C_6H_4CO (**15**)	40	62	59	97

[a] Isomeric ratios (γ/α > 20:1, *E*/*Z* > 20:1). Determined by ^{1}H NMR.

51% (*E*/*Z* 76:24).[27] Although the intramolecular reaction of the corresponding specific substrate with a copper-directing leaving group (−OCONHPh) induced γ-selective substitution via *in situ* formation of a heterocuprate associated with the leaving group (γ/α > 99:1), the product was obtained as an *E*/*Z* mixture (89:11).[28] Furthermore, the construction of the *gem*-diarylalkane structure through γ-selective substitution of cinnamyl alcohol derivatives with an aryl nucleophile has been quite rare. The iridium-catalyzed asymmetric γ-substitution of cinnamyl carbonates with arylzinc reagents reported by Alexakis *et al*. is highly enantioselecive, but the regioselectivities are poor.[29] Recently, Tomioka reported the copper-catalyzed asymmetric γ-substitution of cinnamyl bromides with aryl Grignard reagents, which proceeded with high enantioselectivities and with fairly high γ-selectivities, but the reaction formed significant amounts (3−25%) of α-substitution products.[6c]

To our delight, the reaction of chiral cinnamyl acetate (*S*)-(*E*)-**9** (99% ee) with *p*-methoxyphenylboronic acid (**2b**) in the presence of $Pd(OAc)_2$, 1,10-phenanthroline, and $AgSbF_6$ in THF at 60 °C proceeded with excellent γ- and *E*-selectivities to give the corresponding diarylalkane derivative (*S*)-(*E*)-**16ab**. The absolute configuration of the diarylalkane indicated that the 1,3-*syn*-stereochemistry was retained, but the enantiomeric excess of the product appeared to be slightly decreased compared to that of the starting material (from 99 to 96%; Table 4, entry 1). Lowering the reaction temperature to 40 °C almost prevented the loss of enantiomeric excess, but this in turn caused a considerable decrease in yield (entry 2).

Our investigation of leaving groups revealed that the benzoyloxy group gave a slightly improved yield compared to the acetoxy group (Table 4, entry 3) and that an *ortho*-substituent (MeO, Me, and CF_3) on the benzoyloxy group had a generally beneficial effect in terms of yield improvement, irrespective of electronic effects (entries 4−6). The introduction of two *o*-MeO substituents, however, resulted in a drastic decrease in yield (entry 7), while a MeO substituent at the *para*-position was less effective than at the *ortho*-position (entry 8). Overall, the *o*-methoxybenzoyloxy group turned out to be the best leaving group, affording the highest isolated yield (70%) without any loss of enantiomeric excess during the chirality transfer (entry 4). Furthermore, *o*-methoxybenzoyl chloride, the source of the leaving group, is a salicylic acid derivative and inexpensive. Therefore, we employed this leaving group for further studies of diarylalkane synthesis. The effectiveness of *ortho*-substitution in the leaving group may be associated with the nonplanarity of the aromatic group and the carbonyl group.

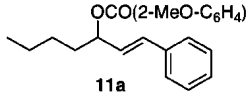
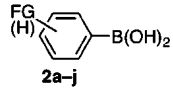
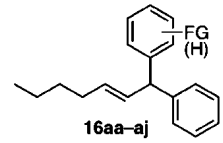
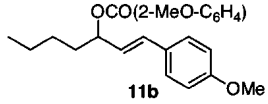
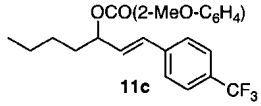
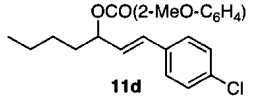
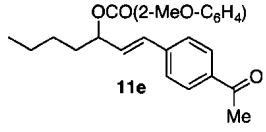
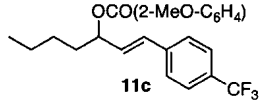
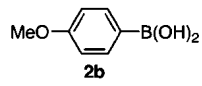
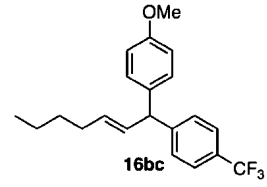
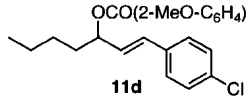
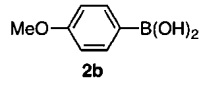
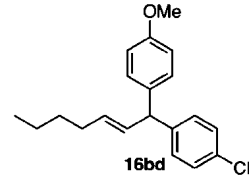
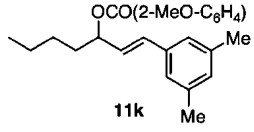
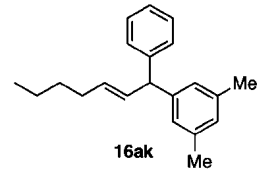
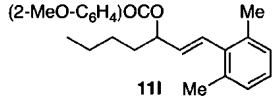
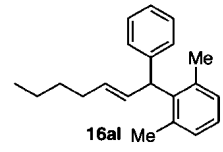
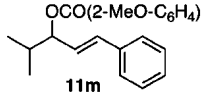
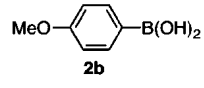
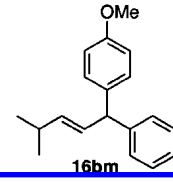
Next, we examined the scope of the transformation using racemic cinnamyl benzoates as substrates (Table 5). The coupling reactions proceeded with excellent regio- (>20:1) and *E*/*Z*- (>20:1) selectivity, regardless of the substitution patterns of the cinnamyl esters. The palladium system was applicable to a broad range of arylboronic acids and cinnamyl alcohol derivatives, giving diverse *gem*-diarylalkanes (entries 2−12). For both arylboronic acids (**2**) and cinnamyl esters (**11b**−**e**), a variety of functional groups, such as MeO, CF_3, chloride, and ketone, were compatible with the synthesis of *gem*-diarylalkanes, while there seemed to be a trend of yield reduction due to the presence of electron-withdrawing substituents on the arylboronic acid.

The *gem*-diarylalkane synthesis showed reasonable tolerance toward steric demand in both arylboronic acid and cinnamyl esters. *o*-Tolylboronic acid (**2g**) was coupled with **11a** in 57% yield with 20 mol % catalytic loading (entry 5). Cinnamyl esters (**11k, l**) with methyl groups at the 3,5- and 2,6-positions of the aromatic ring were also converted to the corresponding *gem*-diarylalkane derivatives in reasonable yields (entries 13 and 14). A bulky substituent such as an isopropyl group was tolerated at the α-position (entry 15).

Formal Total Synthesis of (+)-Sertraline. A concise formal total synthesis of (+)-sertraline (**8**), an important antidepressant agent in clinical use, starting from 2,3-*O*-isopropylidene-L-glyceraldehyde (**17**) demonstrates the applicability of the Pd-catalyzed allyl−aryl coupling reaction (Scheme 4).[30] The starting optically active aldehyde **17**, which is readily available from L-ascorbic acid, was subjected to an *E*-selective Horner−Wadsworth−Emmons-type reaction[31] with (3,4-dichlorophenyl)methylphosphonate **18** to give *E*-alkene **19** in 64% yield (*E*/*Z* > 20:1). Next, three-step manipulation of the diol unit in **19** gave the coupling precursor **20** with 97% ee (*R*) in 80% yield. Palladium-catalyzed allyl−aryl coupling between **20** and phenylboronic acid (**2a**) proceeded cleanly with excellent α-to-γ chirality transfer to afford the desired *gem*-diarylalkane **21** with 96% ee (*R*) in 77% yield. This compound contains all the necessary carbon atoms in the target chiral tetralone intermediate **23**. Next, catalytic hydrogenation and desilylation followed by Jones oxidation produced carboxylic acid **22** in 79% yield (from **21**). Acid-catalyzed cyclization of the chiral carboxylic acid gave tetralone **23** with an enantiomeric excess of 94%. The conver-

(27) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986–3990. See also ref 26b.
(28) (a) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715–721. For related work, see also: (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144–2148. (c) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1985**, *50*, 1597–1599.
(29) Alexakis, A.; Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393–3395.
(30) For syntheses of (+)-sertraline, see: (a) Quallich, G. J. *Chirality* **2005**, *17*, S120–S126. (b) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373–5376. (c) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246–5247. (d) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233–236. See also refs 6c and 29.
(31) Enders, D.; Bartsch, M.; Backhaus, D. *Synlett* **1995**, 869–870.

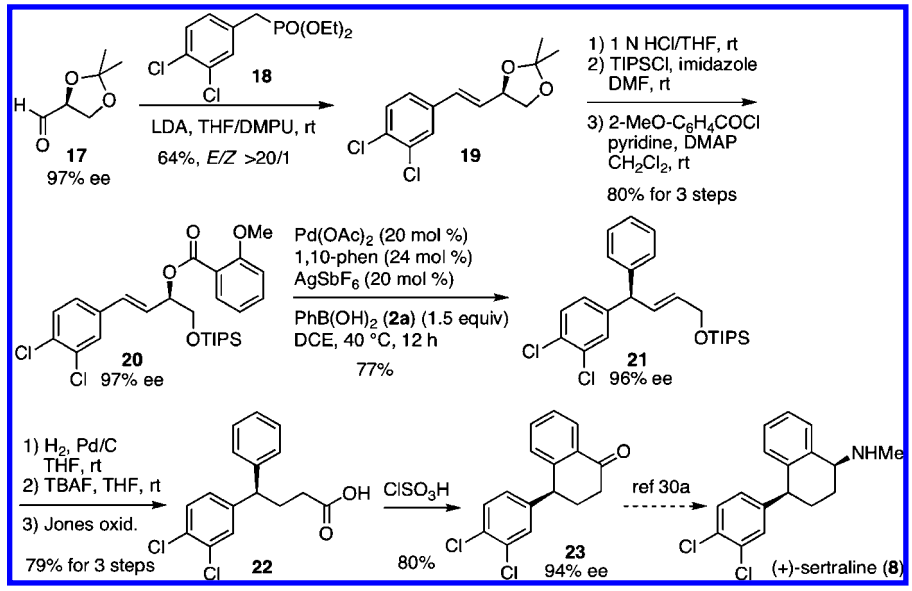
Table 5. Synthesis of *gem*-Diarylalkanes[a]

entry	allylic ester	boronic acid	product		yield[c,d] (%)
1	 **11a**	 **2a–j**	FG = H (**2a**)	 **16aa–aj**	**16aa**	63
2			FG = 4-CF_3 (**2c**)		**16ac**	35
3			FG = 4-Cl (**2d**)		**16ad**	51
4			FG = 4-COMe (**2e**)		**16ae**	34
5[b]			FG = 2-Me (**2g**)		**16ag**	57
6[b]			FG = 3,5-$(OMe)_2$ (**2j**)		**16aj**	74
7[b]	 **11b**		$PhB(OH)_2$ (**2a**)	**16ab**		67
8	 **11c**		$PhB(OH)_2$ (**2a**)	**16ac**		69
9	 **11d**		$PhB(OH)_2$ (**2a**)	**16ad**		65
10[b]	 **11e**		$PhB(OH)_2$(**2a**)	**16ae**		72
11	 **11c**	 **2b**		 **16bc**		58
12	 **11d**	 **2b**		 **16bd**		70
13[b]	 **11k**		$PhB(OH)_2$ (**2a**)	 **16ak**		68
14[e]	 **11l**		$PhB(OH)_2$ (**2a**)	 **16al**		59
15[e]	 **11m**	 **2b**		 **16bm**		61

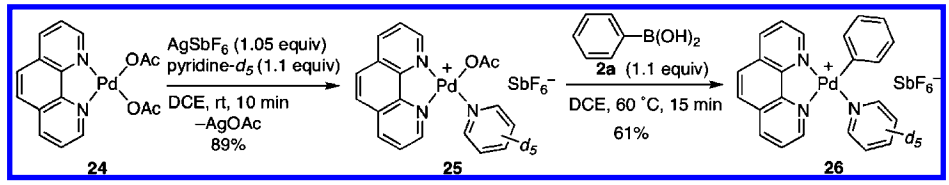
[a] Conditions: $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (12 mol %), $AgSbF_6$ (10 mol %), **11** (0.25 mmol), arylboronic acid (**2**) (0.375 mmol), DCE (1.0 mL), 40 °C, 18 h. [b] Conditions: $Pd(OAc)_2$ (20 mol %), 1,10-phenanthroline (24 mol %), $AgSbF_6$ (20 mol %), **11** (0.25 mmol), arylboronic acid (**2**) (0.375 mmol), DCE (1.0 mL), 40 °C, 18 h. [c] Isolated yield. [d] Isomeric ratios (γ/α > 20:1, *E*/*Z* > 20:1). Determined by ^{1}H NMR. [e] The isolated products were contaminated with traces of unidentified materials (3%).

sion of **23** to (+)-sertraline through reductive amination has been reported previously.[30a] Thus, the chirality derived from L-ascorbic acid was successfully used in the construction of the *gem*-diarylalkane structure in (+)-sertraline (**8**). In addition, all

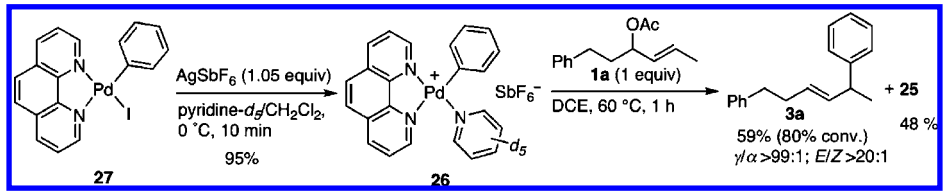
Scheme 4. Synthesis of (+)-Sertraline



Scheme 5. Reaction of Di(acetoxo)palladium(II) Complex **24** and $AgSbF_6$ To Form Mono(acetoxo)palladium(II) Complex **25** and Its Reaction with Phenylboronic Acid (**2a**)



Scheme 6. Preparation of (σ-Phenyl)palladium(II) Comolex **26** and Its Stoichiometric Reaction with Allylic Acetate **1a**



of the carbon atoms in L-ascorbic acid were used as carbon sources in the synthesis of the target molecule.

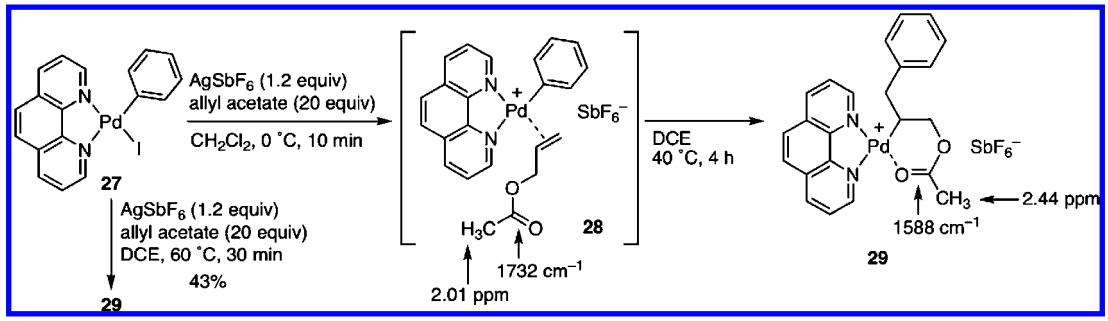
Mechanistic Studies and Proposed Mechanism. To shed light on the mechanism of Pd-catalyzed allyl−aryl coupling, we carried out stoichiometric reactions of palladium complexes that were considered to be relevant to the catalysis (Scheme 5). First, the role of the silver salt was investigated. The reaction of the phenanthroline-ligated $Pd(OAc)_2$ complex **24** with 1.05 equiv of $AgSbF_6$ and 1.1 equiv of pyridine-d_5 in DCE occurred immediately at rt and gave, after filtration and concentration, a mixture containing the cationic mono(acetoxo)palladium(II) complex [Pd(OAc)(phen)(pyridine-d_5)]SbF_6 (**25**) (phen = 1,10-phenanthroline) and small amounts of unidentified materials. The formula for complex **25** was deduced by ^1H, ^{13}C NMR and H−H COSY NMR analysis and HRMS (ESI+, CH_3CN). ^1H NMR (CD_2Cl_2 containing 1% pyridine-d_5) analysis of the crude material indicated that the purity and yield of **25** were 91 and 89%, respectively.

The reactivity of the cationic mono(acetoxo)palladium(II) complex (**25**) toward $PhB(OH)_2$ (**2a**) was then investigated. Complex **25** (91% purity) was treated with $PhB(OH)_2$ (**2a**) (1.1 equiv with respect to **25**) in DCE. No reaction was observed at rt (10 min), but upon heating to 60 °C for 15 min, complex **25** was completely consumed. After the removal of a small amount of insoluble material by filtration, DCE was evaporated, the residue was dissolved in CH_2Cl_2, and Et_2O was added. The resulting almost colorless precipitate was collected and washed with Et_2O. ^1H and ^{13}C NMR and HRMS (ESI+, CH_2Cl_2) indicated that the major component of this material was a cationic (σ-phenyl)palladium(II) complex (**26**) with the formula [Pd(σ-Ph)(phen)(pyridine-d_5)]SbF_6. ^1H NMR analysis using an internal standard indicated that the purity and the yield of **26** are 57 and 61% (based on **25**). The alternative synthesis of complex **26** through a metathesis reaction between the known complex [PdI(σ-Ph)(phen)] (**27**)[32] and $AgSbF_6$ in the presence of pyridine-d_5 confirmed the assignment for **26** (Scheme 6).

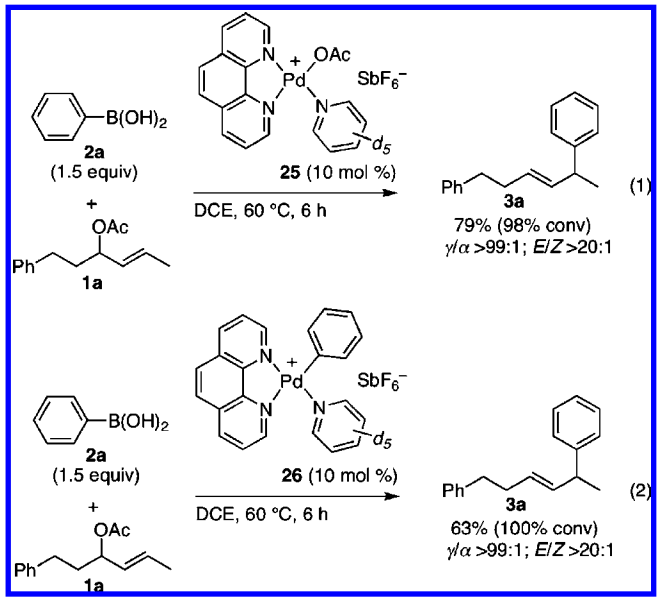
Next, the reaction of the (σ-phenyl)palladium(II) complex (**26**) with allylic acetate **1a** (1 equiv) was investigated (Scheme 6). For this study, pure **26** derived from **27** was used. Specifically, complex **26** reacted with **1a** in DCE at 60 °C and, after 1 h, gave the allyl−aryl coupling product (**3a**) and the acetoxopalladium(II) complex (**25**) in 59 and 48% NMR yields, respectively (the recoveries of **1a** and **26** were 20 and 22%, respectively).

(32) De Felice, V.; de Renzi, A.; Fraldi, N.; Panunzi, B. *Inorg. Chim. Acta* **2009**, *362*, 2015–2019.

Scheme 7. Reactions of a Cationic Palladium(II) Complex and Allyl Acetate

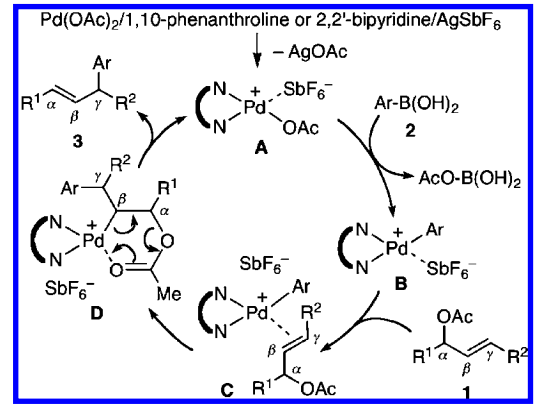


Both the mono(acetoxo)palladium(II) complex (**25**) and the (σ-phenyl)palladium(II) complex (**26**) were capable of being used as catalyst precursors (10 mol %) for allyl−aryl coupling between allylic acetate **1a** and $PhB(OH)_2$ (**2a**) (eqs 1 and 2). The former was as effective as a catalyst prepared from $Pd(OAc)_2$, 1,10-phenanthroline, and $AgSbF_6$ (1:1.2:1) (79% isolated yield), while the reaction catalyzed by the latter resulted in a slightly decreased yield (63%).



We tried to detect a π-complex with **1a** or the resulting carbopalladation product, in the *in situ* NMR observation of the reaction between **26** and **1a**, but in vain. By employing allyl acetate instead of **1a**, however, we were able to observe an intermediary alkene−Pd(II) complex (**28**) and a carbopalladation product (**29**) (Scheme 7). Allyl acetate was selected as a substrate for the isolation studies because we knew its inertness toward the catalytic coupling reaction. Specifically, complex **27** was treated with $AgSbF_6$ (1.2 equiv) and allyl acetate (20 equiv) in CH_2Cl_2 at 0 °C for 10 min. From a filtered and concentrated mixture, a complex consisting of a $[(phen)Pd(Ph)(allyl\ acetate)]^+$ fragment, whose structure is most likely to be depicted in a form of π-complex **28**, was obtained.[33] Because slow conversion from **28** to the carbopalladation product **29** was observed even at 0 °C in CD_2Cl_2, the full characterization of **28** was yet to be successful. The consumption of **28** (mostly into **29**) was completed by heating a solution of **28** in DCE at 40 °C for 4 h. Alternatively, when the reaction of

Scheme 8. Proposed Catalytic Cycle

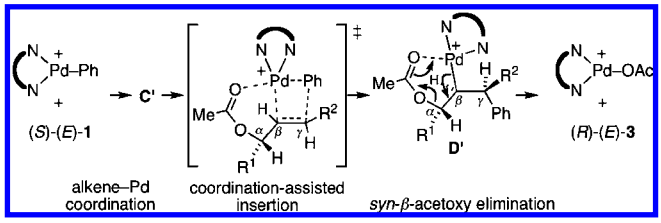


27, $AgSbF_6$, and allyl acetate was carried out at 60 °C, a material containing the carbopalladation product (**29**) as a major component (73% purity) was directly obtained (43% NMR yield for **29**) after filtration, concentration, and precipitation from CH_2Cl_2/Et_2O. The structure of **29** was unambiguously deduced by ^1H and ^{13}C NMR, IR, and ESI-MS spectroscopies. The IR and ^1H NMR spectroscopies clearly indicated that the carbonyl group of the complex **28** is uncoordinated [ν(C═O) 1732 cm^{-1}; δ 2.01 ($COCH_3$)] and that of the carbopalladation product **29** coordinated to the palladium atom [ν(C═O) 1588 cm^{-1}; δ 2.44 ($COCH_3$)]. A trace of β-hydride elimination of the isolated **29** to form (*E*)-cinnamyl acetate was observed, while no β-acetoxy elimination to form allylbenzene proceeded. The resistance of **29** toward the β-acetoxy elimination seems to be due to the lower stability of the resulting monosubstituted alkene compared with that of internal alkenes.

Based on our scenario for γ-selective allylic substitution (Scheme 1d), the results of the catalytic reactions, and the information obtained in the studies of the stoichiometric reactions, we propose a simplified mechanistic model, shown in Scheme 8. First, the reaction of 1,10-phenanthroline-ligated $Pd(OAc)_2$ and $AgSbF_6$ forms the cationic mono(acetoxo)palladium(II) complex **A**. The catalytic cycle is initiated by transmetalation between **A** and an arylboronic acid (**2**) to form the (σ-aryl)palladium(II) intermediate **B**. Subsequently, **B** forms π-complex **C** with an allylic acetate (**1**). The π-complex **C** then undergoes regioselective C−C double bond insertion into the aryl−Pd bond (carbopalladation) with the assistance of intramolecular coordination of the carbonyl oxygen of the acetoxy group to the cationic Pd center, forming metallacyclic alkylpalladium(II) **D**. Finally, β-acetoxy elimination, rather than β-hydride elimination, from **D** affords coupling product **3** and regenerates

(33) The structure of **28** was deduced by ^1H NMR, IR, and HRMS (ESI+, $CHCl_3$) spectroscopies. The ^{13}C NMR measurement was unsuccessful.

Scheme 9. Proposed Mechanism for the 1,3-*syn* Chirality Transfer for the Reaction between (*S*)-(*E*)-**1** and **2a**



A. Notably, alkene products derived from β-hydride elimination of alkylpalladium(II) intermediate **D** were not observed.[34,35]

The stereochemical outcome observed in the reaction of the chiral allylic acetate (*S*)-(*E*)-**1** can be rationalized by considering $A^{1,3}$-strain in the substrate during the coordination-assisted insertion (**C′** to **D′**) and *syn*-β-acetoxy elimination (from **D′**), as shown in Scheme 9. The allylated benzene product with (*Z*)-stereochemistry was not formed even in cases in which a slight loss of enantiomeric purity was observed. The results suggest that the loss of enantiomeric purity was caused by *anti*-attack of **B** to the lower-energy conformer of (*E*)-**1** rather than *syn*-attack to a higher-energy conformer.

As mentioned earlier, our attempts to use the pinacolato ester of phenylboronic acid or alkenylboron compounds as coupling partners with **1a** resulted in no reaction. In view of the proposed catalytic cycle involving B−Pd transmetalation and carbopalladation followed by β-acetoxy elimination, the problem could be in either the transmetalation step or the carbopalladation step. To determine which step was responsible for the resistance to Pd catalysis, we carried out stoichiometric reactions with the cationic mono(acetoxo)palladium(II) complex **25**. The reaction between the pinacolato ester of phenylboronic acid and **25** did not proceed at 60 °C for 1 h. Similarly, both the alkenylboronic acids and their ester derivatives resisted the reaction with **25**. These results strongly suggest that the transmetalation step is the direct cause of the resistance of these organoboron compounds toward the coupling reaction.

Conclusion

We developed a palladium-catalyzed allyl−aryl coupling reaction between acyclic (*E*)-allylic esters and arylboronic acids, which proceeded with excellent γ- and *E*-selectivity. The reaction of optically active allylic esters, derived from readily available allylic alcohols with an α-stereogenic center, took place with excellent α-to-γ chirality transfer and *syn*-selectivity and gave the corresponding optically active allyl−aryl coupling products with benzylic stereogenic centers, which are otherwise difficult to prepare. This stereospecific coupling reaction is applicable to conjugated allylic esters bearing an aromatic ring at the γ-position, producing optically active *gem*-diarylalkanes.

The system is practical for several reasons: (i) a readily available and cheap acetoxy group can be used in the allylic substrate; (ii) the 2-methoxybenzoyl leaving group for the *gem*-diarylalkane synthesis is also low in cost; (iii) the nitrogen-based ligands, such as 1,10-phenanthroline and 2,2′-bipyridine, are much cheaper than phosphorus-based ligands, which are frequently used in palladium-catalyzed reactions; and (vi) the catalytic system tolerates air and water.

The proposed mechanism, involving the addition of a (σ-aryl)palladium(II) intermediate across the C−C double bond of the allylic ester followed by *syn*-β-acyloxy elimination, with the assistance of intramolecular coordination of the acyloxy group to the palladium center, accounts for all of the observed trends in the Pd-catalyzed allyl−aryl coupling reaction and the stoichiometric reactions of the relevant palladium complexes.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) This is contradictory with the reported results of the oxidative Mizoroki−Heck-type arylation of allylic esters with arylboronic acids. See ref 17.

(35) For Mizoroki−Heck-type arylation of allylic acetates with aryl iodides, see: (a) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729–4732.