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Synthetic Methods

Palladium-Catalyzed Chemoselective Allylic Substitution, Suzuki–Miyaura Cross-Coupling, and Allene Formation of Bifunctional 2-B(pin)-Substituted Allylic Acetate Derivatives**

Byeong-Seon Kim, Mahmud M. Hussain, Nusrah Hussain, and Patrick J. Walsh*[a]

Abstract: A formidable challenge at the forefront of organic synthesis is the control of chemoselectivity to enable the selective formation of diverse structural motifs from a readily available substrate class. Presented herein is a detailed study of chemoselectivity with palladium-based phosphane catalysts and readily available 2-B(pin)-substituted allylic acetates, benzoates, and carbonates. Depending on the choice of reagents, catalysts, and reaction conditions, 2-B(pin)-substituted allylic acetates and derivatives can be steered into one of three reaction manifolds: allylic substitution, Suzuki–Miyaura cross-coupling, or elimination to form allenes, all with excellent chemoselectivity. Studies on the chemoselectivity of Pd catalysts in their reactivity with boron-bearing allylic acetate derivatives led to the development of diverse and practical reactions with potential utility in synthetic organic chemistry.

Introduction

One of the most significant impediments to the efficient synthesis of complex natural and non-natural products is the low level of chemoselectivity exhibited by many reagents and catalysts.[1,2] To compensate for poor chemoselectivity, synthetic organic chemists have been forced to design and implement elaborate protecting-group strategies in their construction of complex natural products.[3]

Although considerable effort has been devoted to understanding chemoselectivity with classical reagents, fewer studies have focused on chemoselectivity with transition-metal catalysts. Given the increasing importance of transition-metal-catalyzed reactions in organic synthesis,[4] we set out to optimize and control catalyst chemoselectivity in some of the most synthetically valuable transition-metal-catalyzed reactions, namely, the Tsuji–Trost allylic substitution[5–9] and Suzuki–Miyaura cross-coupling reactions.[10,11] Palladium–phosphane complexes catalyze both reactions, even though the mechanistic pathways are distinct (Figure 1). Allylic substitutions begin with coordination of the substrate to a palladium(0) center to form a π complex (Figure 1, right-hand cycle). Backside attack by the palladium atom on the carbon atom bearing the leaving group in an oxidative ionization generates a π-allyl–palladium complex. External nucleophilic addition to the π-allyl–palladium complex

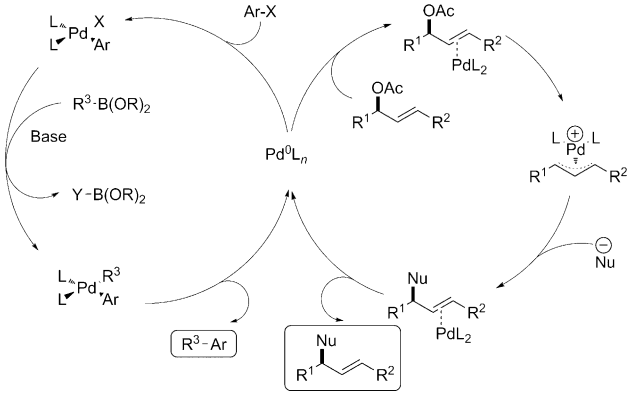

Figure 1. Catalytic cycles of the Tsuji–Trost allylic substitution (right) and Suzuki–Miyaura cross-coupling reaction (left).

followed by liberation of the product regenerates the palladium(0) center. In contrast, the palladium(0) center undergoes oxidative addition in the Suzuki–Miyaura cross-coupling with an aryl halide to form the palladium(II)–aryl halide intermediate (Figure 1, left-hand cycle).[12] Transmetallation with boronic acid derivatives and bases provides the second Pd–C bond.[13] Reductive elimination forms the C–C bond of the product and regenerates the palladium(0) center. More broadly speaking, the palladium atom does not come into contact with the leaving group or nucleophile in the allylic substitution,[14] whereas the palladium center directly interacts with both coupling partners in the Suzuki–Miyaura cross-coupling. The common denominator in these reactions is the ability of the same palladium catalyst to promote both processes.

With this backdrop, we asked a fundamental question: Could the chemoselectivity of a palladium–phosphane-based catalyst toward an allylic acetate, an aryl halide, and a vinyl

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[**] B(pin) = 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl.

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boronate ester be controlled by careful choice of reagents and conditions? This report answers this question and introduces a third orthogonal reaction pathway of 2-B(pin)-substituted (B(pin) = 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) allylic acetates that generates allenes with excellent chemoselectivity. Based on the highly chemoselective reactions developed herein, 2-B(pin)-substituted allylic acetate derivatives are useful "linchpins" that can be utilized for the preparation of an array of small molecules, including functionalized allylic amines and malonates, α-amino ketones, trisubstituted allylic esters and carbonates, and 1,3-disubstituted allenes. A portion of this work related to allylic substitution has been reported previously.[15] Herein, we disclose the scope of the Suzuki–Miyaura cross-coupling and allene formation.

Results and Discussion

The application of multifunctional substrates in tandem reactions enables the rapid construction of diverse chemical arrays. Key to the success of such strategies is the ability to control chemoselectivity by controlling the relative rate of the processes that lead into different reaction manifolds. In this study, we have embedded a vinyl boronate ester in an allylic acetate with the goal of controlling the chemoselectivity between palladium-catalyzed Tsuji–Trost allylic substitution, Suzuki–Miyaura cross-coupling, and allene-forming reactions (Figure 2). Given that the same palladium catalysts promote allylic substitution, cross-coupling, and allene-formation reactions, we focused on reaction conditions and reagents to control the chemoselectivity.

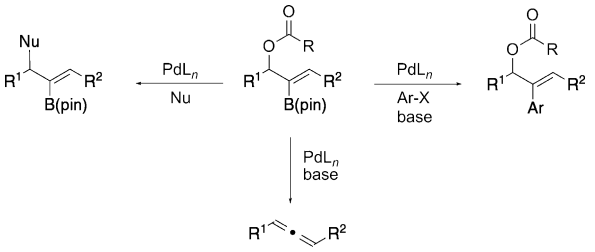
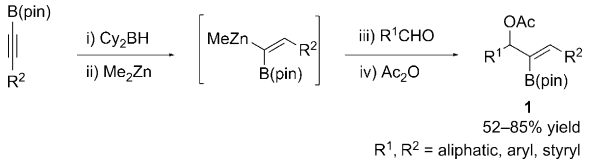


Figure 2. Potential reactions of 2-B(pin)-substituted allylic esters.

Synthesis of 2-B(pin)-substituted allylic acetates

A crucial step toward the development of new synthetic methods is the introduction of reliable and scalable procedures to prepare the substrates. By using our stereodefined 1-alkenyl-1,1-heterobimetallic reagents, the 2-B(pin)-substituted allylic acetates were easily prepared in one pot from readily available alkynyldioxaborolanes (Scheme 1).[15–19] Thus, hydroboration of air-stable alkynyldioxaborolanes with dicyclohexylborane generates 1-alkenyl-1,1-diboro intermediates as the only observable regioisomer (as determined by ^{1}H NMR spectroscopic analysis).[20–26] Although neither B–C bond is very nucleophilic, the boron centers are electronically quite different due to resonance donation from the pinacolato group of the B(pin) substituent. The partially occupied p orbital of the B(pin) boron center dramatically raises the barrier to transmetalation and the vinyl–BCy_2 bond undergoes selective B to Zn transmetalation at −78 °C to generate the heterobimetallic intermediate. The addition of the Zn–C bond to an aldehyde and quenching the resulting alkoxide with acetic anhydride provided 2-B(pin)-substituted (*E*)-allylic acetate **1** in 52–85% yield (Scheme 1). The reaction worked well with linear and branched aliphatic aldehydes (67–85% yield). Likewise, benzaldehyde and its derivatives with electron-withdrawing or electron-donating substituents proved to be good reaction partners (52–78% yield). Cinnamaldehyde gave 60% yield of the rearranged dienyl product formed on isomerization of the acetate moiety (see the Supporting Information). Alkynyldioxaborolanes can be derived from either aliphatic, aromatic, or functionalized alkynes (R^2 = *n*Bu, $(CH_2)_4Cl$, Ph). The scalability of this method was demonstrated in the synthesis of 2-B(pin)-substituted allylic acetates in gram quantities, thus positioning us to explore their reactivity and chemoselectivity with palladium–phosphane-based catalysts.



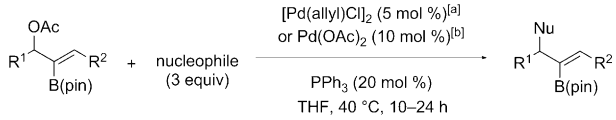
Scheme 1. One-pot synthesis of 2-B(pin)-substituted allylic acetates. Cy = cyclohexyl.

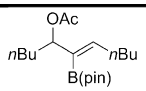
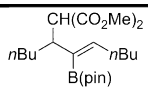
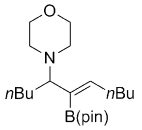
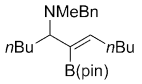
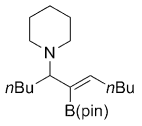
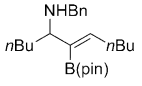
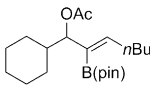
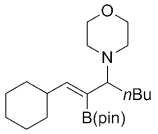
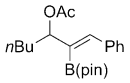
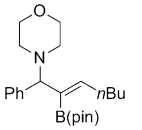
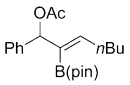
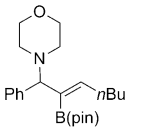
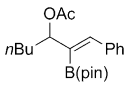
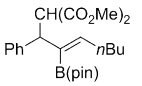
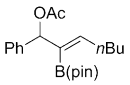
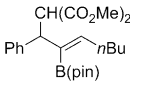
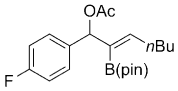
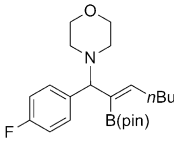
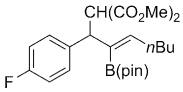
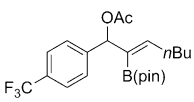
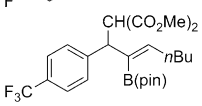
Allylic substitution of 2-B(pin)-substituted allylic acetates: controlling the chemoselectivity

At the outset of our studies, we were concerned about the ability of 2-B(pin)-substituted allylic acetates to successfully undergo the Tsuji–Trost allylic substitution. Although most acyclic allylic acetate substrates are mono- or disubstituted,[7] thus leading to mono or 1,3-disubstituted π-allyl intermediates, the reactivity of 1,2,3-trisubstituted allylic derivatives toward allylic ionization with palladium catalysts has been relatively unexplored.[27–29] A few examples of allylic acetate derivatives containing a boron atom at the 2 position[30,31] have been used in transition-metal-catalyzed allylic substitution reactions,[31] although some examples of 3-boron-substituted analogues have been generated or proposed as intermediates.[32–44] Despite the lack of clear precedent, the conjugate base of dimethylmalonate and several primary and secondary amines participated in allylic substitution. For example, 2-B(pin)-substituted allylic acetate **1a** underwent substitution with sodium dimethylmalonate (Table 1, entry 1) to furnish the 2-B(pin)-substituted allylic alkylation product **2a** in 81% yield. Morpholine, *N*-methylbenzylamine, and piperidine were good substrates that afforded 2-B(pin)-substituted allylic amines **2b–d** in 79–83% yield (Table 1, entries 2–4). Benzyl amine, used as the representative primary amine, also underwent a single allylic substitution to produce **2e** in 65% yield (Table 1, entry 5). The unsymmetrical dialkyl substrate **1c** underwent substitution with morpholine

catalyzed by [{Pd(allyl)Cl}$_2$] and PPh_3 (1:4) with nucleophilic attack at the less-hindered position of the π-allyl unit with excellent regioselectivity (>20:1; Table 1, entry 6). Isomeric 2-B(pin)-substituted allylic acetates **1d** and **1f** each underwent reaction with morpholine and $NaCH(CO_2Me)_2$ by using a catalyst generated from $Pd(OAc)_2$ and PPh_3 (10 and 20 mol%, respectively) to afford the same regioisomer of the allylic substitution products **2g** and **2h** with a regioselectivity of ≥10:1 (Table 1, entries 7–10). The styryl derivative **1d** was less reactive than **1f** toward the same palladium catalyst, thus resulting in lower yields of the substitution products **2g** and **2h** (Table 1, entries 7–10; 45 vs. 80% and 51 vs. 79%, respectively). In contrast to most π-allyl–palladium complexes with a single aryl group at the terminus, allylic substitution took place at the benzylic position in each case. The reversal in regioselectivity is due to formation of the anti aryl π-allyl isomer, which exhibits enhanced reactivity at the benzylic position, as outlined in our related study.[19] Analogous reactions with electron-withdrawing or electron-donating substituents on the aryl groups (**1g–j**) provided the benzylic substitution products **2i–l** in 75–92% yield of the isolated product with a regioselectivity of >10:1 (Table 1, entries 11–14). The unique regioselectivity observed with aryl-substituted substrates enables the synthesis of benzylic amines, which are common structural motifs in medicinal chemistry.[45]

Table 1. Palladium-catalyzed allylic substitution of 2-B(pin)-substituted allylic acetates.



Entry	Acetate		Nucleophile		Product		Yield [%][a]
1		**1a**	$NaCH(CO_2Me)_2$		**2a**	81[b]
2		**1a**			**2b**	83[b]
3		**1a**	HNMeBn		**2c**	80[b]
4		**1a**			**2d**	79[b]
5		**1a**	$BnNH_2$		**2e**	65[b]
6		**1c**			**2f**	60[b,d]
7		**1d**			**2g**	45[c–e]
8		**1f**			**2g**	80[c,d]
9		**1d**	$NaCH(CO_2Me)_2$		**2h**	51[b,d]
10		**1f**	$NaCH(CO_2Me)_2$		**2h**	79[b,d]
11		**1g**			**2i**	75[c,d]
12		**1g**	$CH_2(CO_2Me)_2$		**2j**	90[c,d,f]
13		**1h**	$CH_2(CO_2Me)_2$		**2k**	92[c,d,f]

Development of tandem reactions initiated with allylic substitution

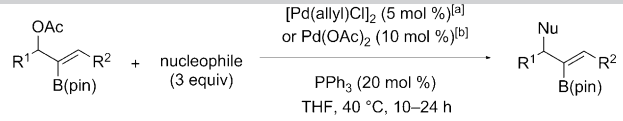
Tandem reactions are important in streamlining organic synthesis, thus enabling a rapid increase in molecular complexity while minimizing synthetic and isolation steps.[46–51] We, therefore, undertook development of tandem processes with 2-B(pin) allylic acetates that began with allylic substitutions and is followed by reactions of the vinyl boronate ester.[52]

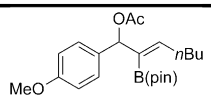
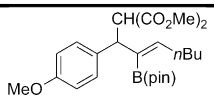
Tandem allylic substitution/oxidation sequences

One of the most utilized transformations of the B–C bond is its oxidation. In the case of vinyl boronate esters, the oxidation products are ketones and allylic substitution/oxidation will lead to α-functionalized ketones. For the tandem allylic substitution/oxidation process, the allylic substitution was performed as outlined in Table 1.

After the allylic substitution, the crude reaction mixture was treated with alkaline hydrogen peroxide to oxidize the B–C bond. When $NaCH(CO_2Me)_2$ was employed as the nucleophile in the substitution, subsequent oxidation generated the substituted ketone **3a** in 85% yield in this one-pot procedure (Table 2, entry 1). Secondary amines performed well in the

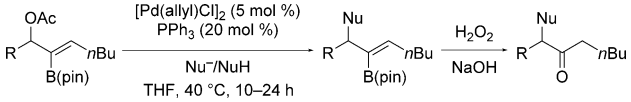
Table 1. (Continued)

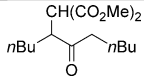
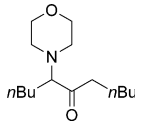
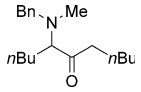
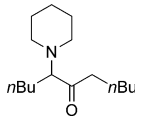
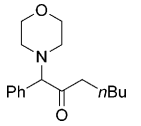


Entry	Acetate		Nucleophile	Product		Yield [%][a]
14		**1j**	$CH_2(CO_2Me)_2$		**2l**	80[c,d,f]

[a] Yield of the isolated and purified products. [b] $[\{Pd(allyl)Cl\}_2]$. [c] $Pd(OAc)_2$. [d] Regioselectivities were $\geq$10:1 (except for entry 6) and were determined by ^1H NMR spectroscopic analysis of unpurified reaction mixtures. [e] Recovered starting material = 30%. [f] Bis(trimethylsilyl)acetamide and catalytic KOAc were used.

Table 2. One-pot synthesis of α-substituted ketones through tandem allylic substitution/oxidation.



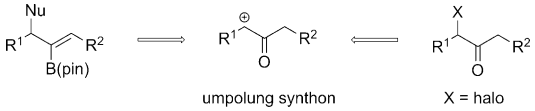
Entry	Allyl acetate	α-Substituted ketones		Yield [%][a]
1	**1a**		**3a**	85
2	**1a**		**3b**	82
3	**1a**		**3c**	81
4	**1a**		**3d**	75
5	**1f**		**3e**	65
6	**1f**		**3e**	78[b]

[a] Yield of the isolated and purified products. [b]Allylic substitution carried out with $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) at room temperature and oxidation carried out with $NaBO_3{\cdot}H_2O$ (3 equiv) in THF/H_2O (1:1) at room temperature.

tandem allylic substitution/oxidation sequence to form α-amino ketones **3b–e** in 65–82% yield (Table 2, entries 2–5). Both aliphatic (Table 2, entries 1–4) and 1-phenyl-2-B(pin)-substituted allylic acetates (Table 2, entries 5 and 6) were good substrates for the tandem process. A milder oxidation with $NaBO_3{\cdot}H_2O$[53,54] resulted in an increased yield of **3e** (Table 2, entry 5 vs. 6).

It is noteworthy that the tandem allylic substitution/oxidation sequence is equivalent to an α-carbonyl cation synthon and represents an umpolung ketone (Scheme 2).[55–59] α-Substituted ketones are difficult to synthesize by using standard π-allyl chemistry. Trost and Gowland demonstrated that 2-alkoxy allylic acetates underwent allylic substitution to afford enol ethers that were hydrolyzed to afford ketones (Scheme 3A).[55] Organ et al. performed similar chemistry with allylic phenoxides (Scheme 3B).[59]

Enantioenriched allylic amines are valuable synthetic intermediates and are common in natural products and compounds with biological activity.[45,60] One possible approach to access such compounds is through allylic substitution of enantioenriched 2-B(pin)-substituted allylic acetates. With this approach in mind, 2-

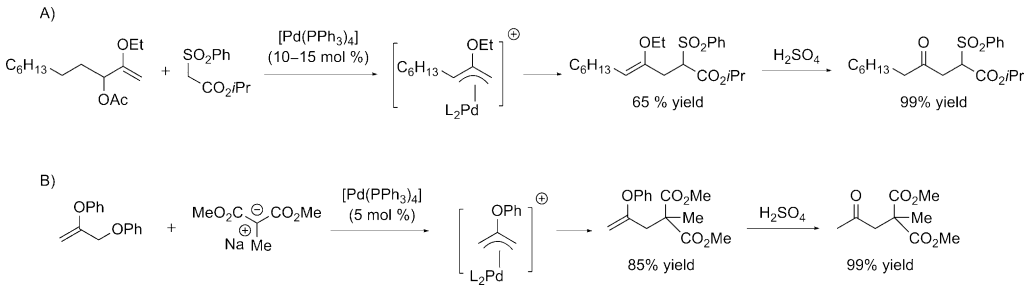


Scheme 2. 2-B(pin)-substituted allylic substitution products as synthons for α-electrophilic carbonyl substrates.

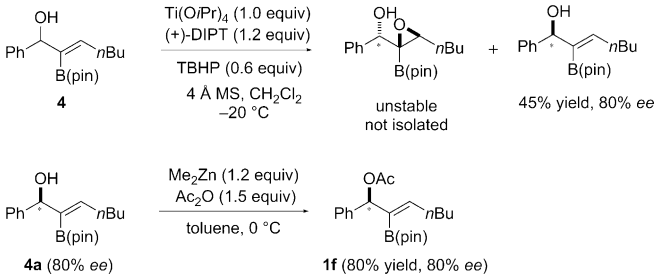
B(pin)-substituted allylic acetate **1f** of 80% *ee* was prepared using the Sharpless–Katsuki kinetic resolution[61] of 2-B(pin) allylic alcohol **4a**[16] and subsequent acetylation with acetic anhydride (Scheme 4).[15] We then conducted an allylic substitution of **1f** and morpholine to form 2-B(pin)-substituted benzylamine **2b** in 82% yield without loss of enantiomeric excess (Scheme 5). A tandem allylic substitution/B–C bond oxidation with $NaBO_3{\cdot}H_2O$ generated the α-amino ketone with 77% *ee* in 80% yield (Scheme 5). Unfortunately, by employing alkaline H_2O_2 in place of $NaBO_3{\cdot}H_2O$ for the oxidation led to racemization of the amino ketone product.

Tandem allylic substitution/Suzuki–Miyaura cross-coupling

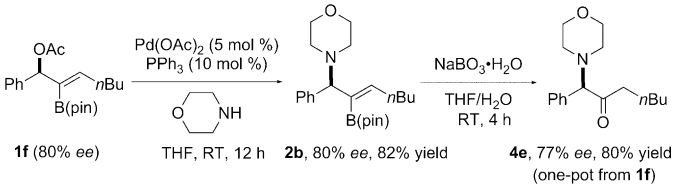
Allylic amines are present in molecules with diverse pharmacological properties, such as Acrivastine (Semprex),[45,62] Flunarizine (Sibelium, Ca-channel blocker),[63,64] and several γ-aminobutyric acid (GABA) uptake inhibitors.[65] In the synthesis of allylic amines, it is usually important that the geometry about the C=C bond can be controlled to provide a single product. With that aim in mind, we sought to achieve a one-pot allylic substitution/Suzuki–Miyaura cross-coupling reaction of 2-B(pin)-substituted allylic acetates. As alluded to in Figure 1, it is conceivable that the allylic substitution and Suzuki–Miyaura cross-coupling could be catalyzed with the same palladium source. One of the key factors to turn on the Suzuki–Miyaura cross-coupling will be the activation of the B–C bond, initiated by hydrolysis to the boronic acid group. It is noteworthy that a successful allylic substitution/cross-coupling sequence enables the synthesis of a variety of 2-arylated allylic amines and malonates from easily accessible 2-B(pin)-substituted allylic acetates, aryl halides, amines, and malonates. The allylic substitution of 2-B(pin) allylic acetate **1a** and morpholine was performed following the conditions given in entry 8 of Table 1.



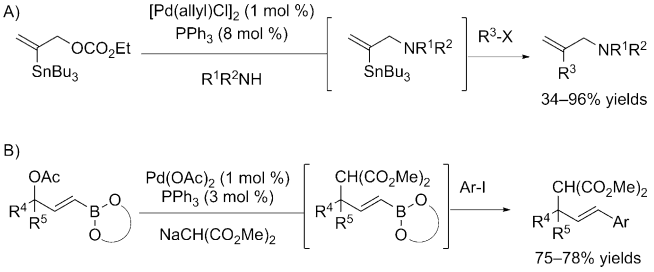
Scheme 3. Trost's (A) and Organ's (B) approach to access ketone surrogates via allylic substitution reaction of 2-alkoxy substituted allylic acetates and phenoxides.



Scheme 4. Kinetic resolution of 2-B(pin)-substituted allylic alcohol **4** to prepare enantioenriched 2-B(pin)-substituted allylic acetate **1 f**. DIPT = *N*,*N*-diisopropyltryptamine, TBHP = *tert*-butyl hydroperoxide.



Scheme 5. Allylic substitution of enantioenriched **1 f** with morpholine followed by oxidation with sodium perborate.



Scheme 6. A) One-pot allylic amination/Stille coupling reaction developed by Kazmaier and co-workers. B) Tandem Tsuji–Trost allylic substitution/Suzuki–Miyaura cross-coupling reaction developed by Pucheault and co-workers.

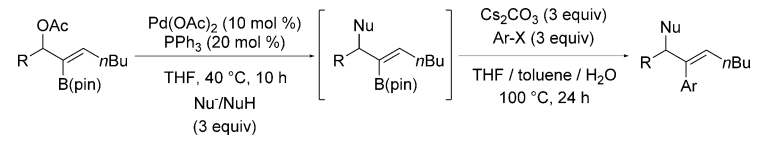
After completion of the substitution, as judged by TLC analysis, the reaction mixture was diluted with THF/water (10:1, v/v) and then Cs_2CO_3, and aryl halide were added to the reaction mixture, which was heated (Table 3). After workup, the 2-arylated trisubstituted allylic amine derivatives **5 a**–**c** were isolated in 52–70% yield (Table 3, entries 1–3), including the 3-pyridyl derivative. Likewise, unsymmetrical 2-B(pin)-substituted allylic acetate **1 f** underwent the tandem allylic substitution with morpholine/cross-coupling to yield trisubstituted benzylic amines **5 d**–**f** in 50–70% yield (Table 3, entries 4–7). Aryl bromide coupling partners with electron-donating or electron-withdrawing substituents were well tolerated. Iodobenzene gave a lower yield than the aryl bromides (Table 3, entries 4 and 5). Tandem Suzuki–Miyaura cross-coupling of the allylic substitution product **2 h** with sodium malonate failed with iodobenzene, leading to recovery of the allylic substitution product **2 h** (43% yield; Table 3, entry 8). In contrast, **1 f** and **1 h** underwent tandem allylic substitution with $NaCH(CO_2Me)_2$/cross-coupling with bromobenzene in 51 and 61% yield (Table 3, entries 9 and 10). Importantly, in all cases, the geometry of the double bond was maintained.

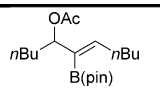
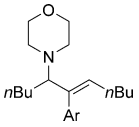
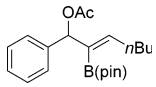
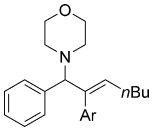
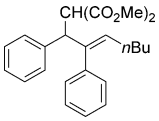
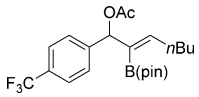
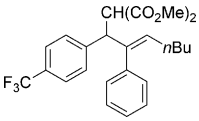
Related palladium-catalyzed tandem reactions have been reported by the groups of Kazmaier and Pucheault. Kazmaier and co-workers established one-pot allylic amination/Stille couplings of β-stannylated allylic carbonates to provide allylic amine derivatives (Scheme 6 A).[66,67] This approach provides disubstituted allylic amines and is complementary to the chemistry shown in Table 3, which generates trisubstituted products. After our initial report,[15] Pucheault and co-workers followed with a tandem palladium-catalyzed Tsuji–Trost allylic substitution/Suzuki–Miyaura cross-coupling of γ-borylated allylic acetates (Scheme 6 B).[42] This reaction provides traditional allylic substitution products that can be generated in an efficient tandem fashion. With respect to the synthesis of compound libraries, our approach furnishes 1,2,3-trisubstituted allyl products, which contain an additional point of diversity over those in Scheme 6. To expand the synthetic utility of 2-B(pin)-substituted allylic ester derivatives further, we set out to reverse the chemoselectivity by performing the Suzuki–Miyaura cross-coupling in the presence of the allylic ester derivatives.

Chemoselective Suzuki–Miyaura cross-coupling in the presence of allylic leaving groups

As demonstrated in Tables 1–3, allylic substitutions of 2-B(pin)-substituted allylic acetates proceed readily despite the large size of the B(pin) group. We asked the question whether the

Table 3. Tandem allylic substitution/Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates.



Entry	Allyl acetate	Nu⁻/NuH	Ar-X	Product	Yield [%][a]
1		**1a**	4-Me-C_6H_4-Br		**5a** 70
2		**1a**	4-MeO-C_6H_4-Br		**5b** 65
3		**1a**	3-C_5H_3N-Br		**5c** 52
4		**1f**	Ph-I		**5d** 50
5		**1f**	Ph-Br		**5d** 70
6		**1f**	4-MeO-C_6H_4-Br		**5e** 69
7		**1f**	4-O_2N-C_6H_4-Br		**5f** 59
8		**1f** $NaCH(CO_2Me)_2$	Ph-I		–[b]
9		**1f** $NaCH(CO_2Me)_2$	Ph-Br		**5g** 51
10		**1h** $NaCH(CO_2Me)_2$	Ph-Br		**5h** 61

[a] Yield of the isolated and purified products. [b] No cross-coupling product was observed, but 43% of **2h** was isolated.

Suzuki–Miyaura cross-coupling reaction could be conducted in the presence of the allylic ester derivatives. The determining factor that controls the bifurcation between the two reaction manifolds is the relative rate of oxidative ionization of the allylic ester versus the oxidative addition of the aryl halide (Figures 1 and 2). Although there have been many studies on the oxidative addition of aryl and vinyl halides and numerous investigations into the oxidative ionization of allylic acetates,[12,14] very few studies compare the relative rates of these two processes.[68–71] As pointed out by Organ et al.,[59,72] in cases in which a comparison was made, the substrates employed were frequently biased by either steric effects or conformational restrictions that disfavor the proper orbital alignment needed for the allylic ionization to proceed.

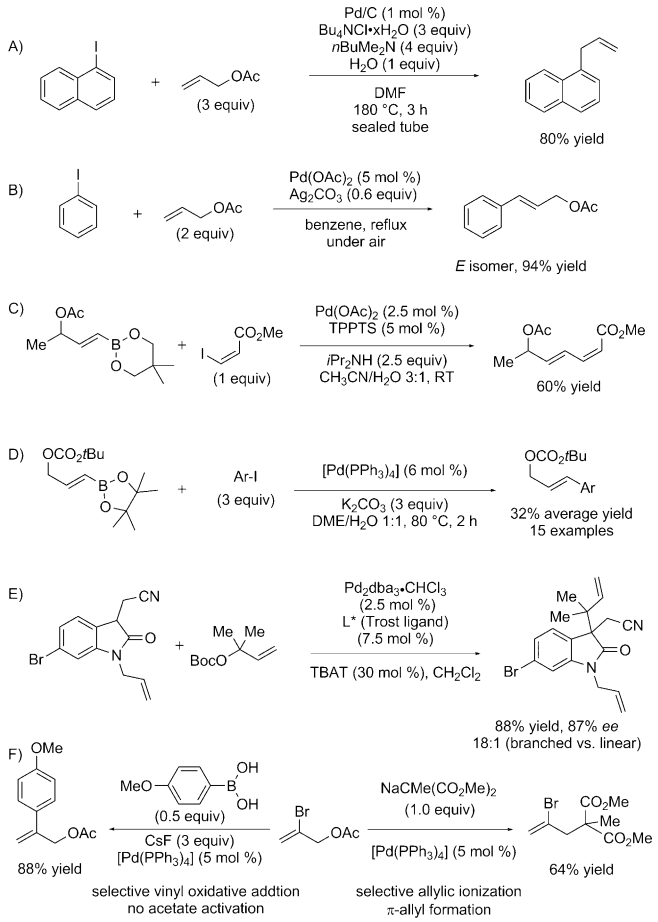
Precedents for the oxidative addition of aryl halides in the presence of allylic acetates

The chemoselectivity of palladium-based catalysts has been investigated by several groups.[73–76] Lautens et al. developed a reductive coupling of allylic acetates that involves β-OAc elimination (Scheme 7A).[77,78] Jiao and co-workers demonstrated a complementary Heck reaction of allylic acetates that undergo traditional β-hydride elimination rather than β-acetate elimination (Scheme 7B).[79] Genet and co-workers conducted a chemoselective Suzuki–Miyaura cross-coupling reaction of γ-borylated allylic acetates with activated alkenyl iodides (Scheme 7C).[80] Kočovský and co-workers investigated a Suzuki–Miyaura cross-coupling reaction of simple γ-borylated allylic carbonates with aryl iodides (Scheme 7D).[39] The cross-coupling products were isolated in low-to-moderate yields (32% average yield for 15 substrates), and the reactions failed with aryl bromides. Although the conditions and catalysts used in Scheme 7A–D are different, the trend suggests that an oxidative addition of sp^2 C–I bonds is faster than ionization of allylic acetates, but the increased reactivity of carbonates results in low cross-coupling yields (Scheme 7D).

In the case of aryl bromides, Trost, Malhotra, and Chan recently found that *tert*-butoxycarbonyl (Boc)-activated allylic alcohols undergo allylic substitution in the presence of an aryl bromide (Scheme 7E).[81] Interestingly, Organ et al. demonstrated that the same palladium catalyst can be used to selectively afford either the allylic substitution or vinylic cross-coupling products from polyfunctionalized olefin building blocks (Scheme 7F).[59,72] Due to the diverse substrates, catalysts, and conditions employed in Scheme 7, only a fragmented picture of the reactivity landscape is provided. A systematic study is necessary to map the relative reactivity of aryl halides in the Suzuki–Miyaura cross-coupling in the presence of allylic ester derivatives of varying reactivity.

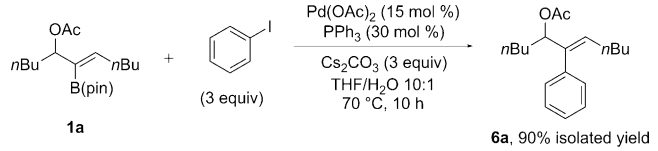
Development of orthogonal reaction conditions for the palladium-catalyzed allylic substitution and Suzuki–Miyaura cross-coupling

To favor the Suzuki–Miyaura cross-coupling manifold, the palladium(0) form of the catalyst would need to be rapidly captured by the aryl halide. It is well known that the relative rate of oxidative addition of a homologous series of aryl halides is Ar-I > Ar-Br > Ar-Cl.[12,13] We envisioned that an aryl iodide would rapidly undergo oxidative addition to a Pd^0 center to generate a Pd^{II}–aryl iodide intermediate, which is unreactive toward oxidative ionization of the allylic acetate (Figure 1). To



Scheme 7. Precedents for the oxidative addition of aryl halides in the presence of allylic acetates (see the text for discussion; dba = dibenzylideneacetone).

explore the possibility of conducting the Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates, the di-*n*-butyl substrate **1a** was combined with iodobenzene, $Pd(OAc)_2$ (15 mol%), PPh_3 (30 mol%), and Cs_2CO_3 (3 equiv) in a THF/water reaction mixture (10:1; Scheme 8). A clean reaction occurred at 70 °C to generate 2-aryl-substituted allylic acetate **6a** in 90% yield of the isolated product. The cross-coupling was incomplete and gave diminished yields at lower catalyst loading. We set out to optimize the Suzuki–Miyaura cross-coupling reaction of 2-B(pin)-substituted allylic acetates to lower the catalyst loading, increase the yields, and develop a broad substrate scope (Scheme 8).



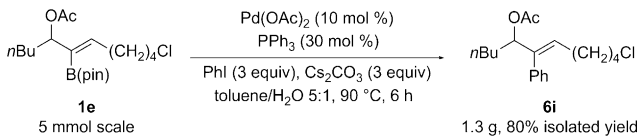
Scheme 8. Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetate **1a**.

Optimization of Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates

Lowering the catalyst loading from 15 (Scheme 8 and Table 4, entry 1) to 10 mol% Pd resulted in decreased yield of the cross-coupled product **6a** (Table 4, entry 2). To optimize the coupling, different phosphane ligands were employed. The bulky P(*o*-Tol)$_3$ led to formation of the product in only 20% yield (Table 4, entry 3). Bidentate phosphane ligands gave poor yields of the arylated allylic acetates (27–62% yield; Table 4, entries 4–6). Subjecting the di-*n*-butyl allylic acetate **1a** to various Pd precursors showed that $Pd(OAc)_2$/P(*t*Bu)$_3$, [$Pd(PPh_3)_4$], and [$PdCl_2(PPh_3)_2$]/PPh_3 all formed suitable catalysts for the chemoselective activation of iodobenzene versus oxidative ionization of the allylic acetate (Table 4, entries 7–9). Several bases were screened (i.e., Cs_2CO_3, CsF, and K_3PO_4), of which Cs_2CO_3 gave the highest yield (Table 4, entries 10–12). When toluene was used in place of THF or dioxane, the catalyst loading could be lowered to 5 mol% with shorter reaction times and up to 96% yield (Table 4, entries 13–16). Further decreasing the catalyst loading, however, led to incomplete reactions and lower yields. A 1:3 ratio of $Pd(OAc)_2$ to PPh_3 was optimal for catalyst formation (95–96% yield; Table 4, entries 13 and 14) and suitable for evaluation of the scope of the cross-coupling reaction.

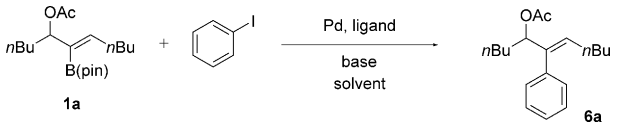
Substrate scope of Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates with aryl iodides

To determine the substrate scope for the Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates, we decided to vary the allylic acetate (R^1 and R^2) and the coupling partner (Ar–I). Aliphatic 2-B(pin)-substituted allylic acetate **1a** cleanly provided the arylated allylic acetates **6a–c** in good-to-excellent yields with several aryl iodides bearing electron-withdrawing or electron-donating groups (60–96% yield; Table 5, entries 1–3). α-Branching is tolerated in the allylic acetate, as shown from the reaction of the allylic acetate **1b** with iodobenzene (67% yield; Table 5, entry 4). The styryl-derived allylic acetate **1d** gave 92–99% yield of the cross-coupled products **6e** and **6f** (Table 5, entries 5 and 6). The isomeric allylic acetate **1f** gave the Suzuki–Miyaura cross-coupled products **6g** and **6h** in 70–75% yield (Table 5, entries 7 and 8). The isomeric pairs in entries 5 and 7 and entries 6 and 8 (Table 5) each undergo Suzuki–Miyaura cross-coupling with no scrambling of the acetate position. These results indicate that the oxidative ionization of the acetate unit is not reversible or does not disrupt a tight ion pair under these conditions.[14]



Scheme 9. Gram-scale Suzuki–Miyaura cross-coupling reaction of **1e**.

Table 4. Optimization of Pd-catalyzed Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetate **1a**.



Entry	Pd/ligand[a]	Base[b]	Solvent[c]	Conc. [M][d]	*t* [h]	Yield [%][e]
1	$Pd(OAc)_2/PPh_3$ (15 mol%, 1:2)	Cs_2CO_3	THF	0.022	24	90[f]
2	$Pd(OAc)_2/PPh_3$ (10 mol%, 1:2)	Cs_2CO_3	THF	0.022	48	62
3	$Pd(OAc)_2/P(o\text{-Tol})_3$ (10 mol%, 1:2)	Cs_2CO_3	THF	0.022	48	20
4	$Pd(OAc)_2$/DPPP (10 mol%, 1:1)	Cs_2CO_3	THF	0.022	48	32
5	$Pd(OAc)_2$/DPPE (10 mol%, 1:1)	Cs_2CO_3	THF	0.022	48	27
6	$Pd(OAc)_2$/DPPF (10 mol%, 1:1)	Cs_2CO_3	THF	0.022	48	62
7	$Pd(OAc)_2/P(t\text{Bu})_3$ (10 mol%, 1:1)	Cs_2CO_3	THF	0.022	48	80
8	$[Pd(PPh_3)_4]$ (10 mol%)	Cs_2CO_3	THF	0.022	36	87
9	$[PdCl_2(PPh_3)_2]/PPh_3$ (10 mol%, 1:1)	Cs_2CO_3	THF	0.08	24	71
10	$[PdCl_2(PPh_3)_2]/PPh_3$ (10 mol%, 1:1)	Cs_2CO_3	dioxane	0.08	18	61
11	$[PdCl_2(PPh_3)_2]/PPh_3$ (10 mol%, 1:1)	CsF	dioxane	0.08	18	25
12	$[PdCl_2(PPh_3)_2]/PPh_3$ (10 mol%, 1:1)	K_3PO_4	toluene	0.08	24	52
13	$Pd(OAc)_2/PPh_3$ (10 mol%, 1:3)	Cs_2CO_3	toluene	0.17	4	96[f]
14	$Pd(OAc)_2/PPh_3$ (5 mol%, 1:3)	Cs_2CO_3	toluene	0.17	18	95[f,g]
15	$[PdCl_2(PPh_3)_2]/PPh_3$ (5 mol%, 1:1)	Cs_2CO_3	toluene	0.17	18	93[f,g]
16	$[Pd(PPh_3)_4]$ (10 mol%)	Cs_2CO_3	toluene	0.17	18	96[f,g]

[a] The mol% of Pd is given with the molar ratio of Pd/phosphane in parenthesis. [b] Three equivalents of base and iodobenzene were used unless otherwise noted. [c] Solvent/H_2O = 10:1. [d] Ratio of **1a** (mmol)/solvent (mL). [e] Yield was determined by integration of the ^1H NMR spectra of the crude reaction mixture with 1,4-dimethoxybenzene as an internal standard. [f] Yield of the isolated and purified products. [g] Two equivalents of Cs_2CO_3 and iodobenzene were used. DPPE = 1,2-bis(diphenylphosphino)ethane, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, DPPP = 1,3-bis(diphenylphosphino)propane.

To demonstrate scalability of the Suzuki–Miyaura cross-coupling 2-B(pin)-substituted allylic acetates, **1e** was subjected to cross-coupling conditions on a scale of 5 mmol to give 1.3 grams of the 2-arylated allylic acetate **6i** in 80% isolated yield (Scheme 9). Given that aryl iodides react faster with palladium(0) than allylic acetates, we next examined less reactive aryl bromides.

Substrate scope of Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates with aryl bromides

We are aware of one study that compared the relative reactivity of sp^2 C–Br bonds versus allylic acetates with palladium catalysts. Organ et al. demonstrated that the preference of the palladium center was dependent on the nucleophile (Scheme 7F).[72]

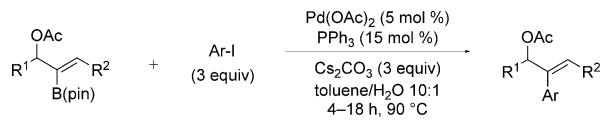
Subjecting the 2-B(pin)-substituted allylic acetates to the Suzuki–Miyaura conditions employed in entry 13 of Table 4 with various aryl and heteroaryl bromides resulted in chemoselective activation of the aryl bromides over the allylic acetates. The substituents on the allylic acetate (R^1 and R^2) and the aryl bromide coupling partners (Ar–Br) were varied to determine the scope of the chemoselective cross-coupling (Table 6). 2-B(pin)-substituted aliphatic allylic acetate **1a** underwent cross-coupling with aryl bromides bearing electron-withdrawing or electron-donating groups with *para* and *ortho* substitution to provide the arylated allylic acetates **6a–c**, **6j**, and **6k** in moderate-to-excellent yields (54–91% yield; Table 6, entries 1–5). α-Branching is tolerated, as shown in the reaction of the allylic acetate **1b** with bromobenzene (87% yield; Table 6, entry 6). The styryl-derived allylic acetate **1d** gave an excellent yield of the cross-coupled product **6f** with 1-bromo-4-nitrobenzene (90% yield; Table 6, entry 7).

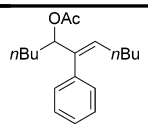
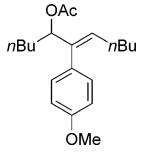
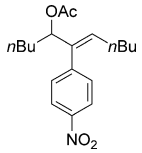
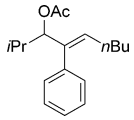
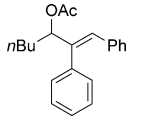
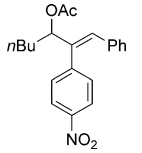
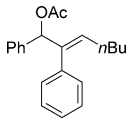
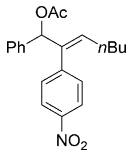
With the isomeric allylic acetate **1f**, the Suzuki–Miyaura cross-coupled product **6h** was obtained in 80% yield (Table 6, entry 8) with no observed scrambling of the acetate position. Heteroaryl bromides such as 2- or 3-bromothiophene underwent cross-coupling with **1a** in 74–82% yield (Table 6, entries 9 and 10). Having demonstrated that aryl iodides and bromides undergo oxidative addition faster than 2-B(pin)-substituted allylic acetates undergo oxidative ionization under these conditions, we wanted to determine whether this trend would continue to hold with more reactive allylic substrates.

Substrate scope of Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic benzoates and carbonates

To delineate further how differences in the substrate reactivity impact the reaction outcome, we turned our attention to increasing the reactivity of the allylic moiety by using more active leaving groups. Allylic benzoates and carbonates are known to be more reactive in allylic substitutions than acetates, with carbonates up to 200 times more reactive than acetates.[14] We, therefore, prepared several 2-B(pin)-substituted allylic benzoates and carbonates from the parent di-*n*-butyl-2-B(pin)-substituted allylic alcohol (see the Supporting Information). The 2-B(pin)-substituted allylic benzoates and carbonates were subjected to the optimal cross-coupling reaction conditions given in entry 13 of Table 4 with aryl iodides and bromides. 2-B(pin)-substituted allylic benzoate **7a** underwent cross-coupling with iodobenzene to furnish 2-aryl substituted allylic benzoate **9a** in 96% yield (Table 7, entry 1). Bromobenzene, on the other hand, resulted in low yield of the cross-coupled product **9a** (38%), with multiple byproducts (Table 7, entry 2). The palladium catalyst likely activates the allylic benzoate in the presence of the less reactive bromobenzene. Electron-deficient aryl halides are known to undergo oxidative addition more rapidly than analogous electron-rich aryl halides.[82–85] With 4-trifluoromethylbromobenzene and allylic benzoate **7a** the cross-coupled product **9b** was isolated in 76% yield (Table 7, entry 3). The 2-B(pin)-substituted allylic carbonates **8a** and **8b** underwent cross-coupling with both aryl iodides and electron-deficient bromides to furnish the 2-arylated allylic carbonates **9c–f** in 57–91% yield (Table 7, entries 4–8). These results demonstrate that the palladium catalyst preferentially oxidatively adds aryl iodides and bromides over 1,3-dialkyl-substituted 2-B(pin) allylic benzoates and carbonates. However, the more reactive 1-phenyl-2-B(pin)-substituted allylic benzoate **7b** and

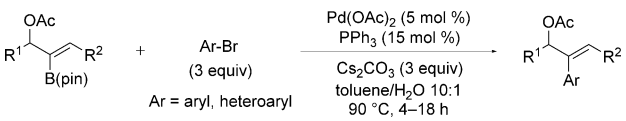
Table 5. Chemoselective Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates with aryl iodides.

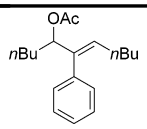
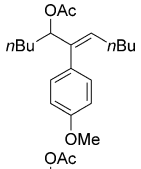
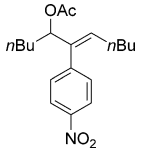
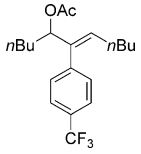
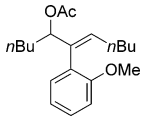
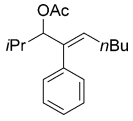
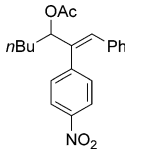
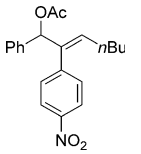
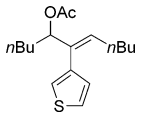
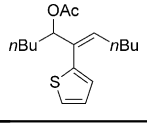


Entry	Acetate	Ar-I	Product		Yield [%][a]
1	**1a**	Ph-I		**6a**	96
2	**1a**	4-MeO-C_6H_4-I		**6b**	60
3	**1a**	4-O_2N-C_6H_4-I		**6c**	92
4	**1b**	Ph-I		**6d**	67
5	**1d**	Ph-I		**6e**	99
6	**1d**	4-O_2N-C_6H_4-I		**6f**	92
7	**1f**	Ph-I		**6g**	70[b]
8	**1f**	4-O_2N-C_6H_4-I		**6h**	75[b]

[a] Yield of the isolated and purified products. [b] The reaction was conducted at 75 °C in THF/H_2O (10:1).

Table 6. Chemoselective Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic acetates with aryl bromides.



Entry	Acetate	Ar-Br	Product		Yield [%][a]
1	**1a**	Ph-Br		**6a**	73
2	**1a**	4-MeO-C_6H_4-Br		**6b**	54
3	**1a**	4-O_2N-C_6H_4-Br		**6c**	91
4	**1a**	4-F_3C-C_6H_4-Br		**6j**	85
5	**1a**	2-MeO-C_6H_4-Br		**6k**	80
6	**1b**	Ph-Br		**6d**	87
7	**1d**	4-O_2N-C_6H_4-Br		**6f**	90
8	**1f**	4-O_2N-C_6H_4-Br		**6h**	80[b]
9	**1a**			**6l**	74
10	**1a**			**6m**	82

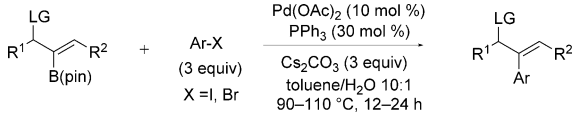
[a] Yield of the isolated and purified products. [b] The reaction was conducted at 75 °C in THF/H_2O (10:1).

carbonate **8c** decomposed, and no cross-coupling product was observed (Table 7, entries 9 and 10).

Chemoselective allene formation from 2-B(pin)-substituted allylic acetates, benzoates, and carbonates

The efficiency of Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allylic substrates is related to the ability of the allylic leaving group to ionize under palladium catalysis (Table 7). Reactive substrates toward allylic ionization, such as benzoate, carbonates, or substrates with benzylic acetates (Table 7, entries 9 and 10) tended to yield less cross-coupling products and more decomposition products. ^{1}H NMR spectroscopic anal-

Table 7. Chemoselective Suzuki–Miyaura cross-coupling of 2-B(pin)-substituted allyl benzoates and carbonates.



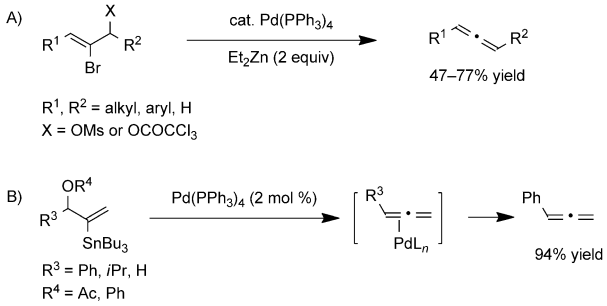
Entry	2-B(pin)-substituted allyls		Ar-Br	Product		Yield [%][a]
1		**7a**	Ph-I		**9a**	96
2		**7a**	Ph-Br		**9a**	38
3		**7a**	4-F_3C-C_6H_4-Br		**9b**	76
4		**8a**	Ph-I		**9c**	91
5		**8a**	4-NO_2-C_6H_4-I		**9d**	78
6		**8a**	4-NO_2-C_6H_4-Br		**9d**	75
7		**8a**	4-CF_3-C_6H_4-Br		**9e**	57
8		**8b**	Ph-I		**9f**	83
9		**7b**	Ph-I			–[b]
10		**8c**	Ph-I			–[b]

[a] Yield of the isolated and purified products. [b] Starting materials decomposed. LG = leaving group.

ysis of unpurified reaction mixtures suggested that decomposed products included allenes and dienes. We hypothesized that the diene products were generated from the allene through palladium-catalyzed isomerization or carbopalladation reactions.[86] If this hypothesis is correct, a third manifold of reactivity might be tapped to afford an additional family of products from 2-B(pin)-substituted allylic ester derivatives. We, therefore, set out to identify catalysts to promote the chemoselective elimination of 2-B(pin)-substituted allylic substrates to provide internal allenes, which are important synthetic intermediates and common in natural products.[87–93]

Precedents for a catalytic 1,2-elimination to form allenes

Tanaka and co-workers reported the conversion of 2-bromo allylic mesylate derivatives into allenes with a catalytic amount of palladium and 2 equivalents of diethylzinc as a reducing agent (Scheme 10 A).[94] More recently, Kazmaier and co-workers demonstrated that β-stannylated allylic acetates or phenoxides undergo 1,2-elimination reactions to provide Pd–allene intermediates, from which terminal allenes were isolated (Scheme 10 B).[95,96] An advantage of our 2-B(pin)-substituted allylic acetates is that they do not require stoichiometric reducing agents or highly reactive mesylates and they provide 1,3-disubstituted internal allenes.

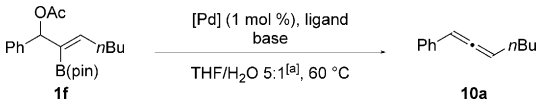


Scheme 10. A) Palladium-catalyzed elimination reaction with diethylzinc developed by Tanaka and co-workers. B) 2-Sn(nBu)$_3$ elimination of 2-stannylated allylic acetates and phenoxides to form terminal allenes developed by Kazmaier and co-workers.

Optimization of allene formation

We set out to screen a variety of palladium precursors and ligands to identify catalysts that would favor allene formation from 1-phenyl-2-B(pin)-substituted allylic acetate **1f**. Subjecting **1f** to catalytic [Pd(PPh_3)$_4$] in THF/H_2O (5:1) at 60 °C resulted in 20% consumption of **1f** with no allene formation, as determined by ^{1}H NMR spectroscopic analysis (Table 8, entry 1). The use of stoichiometric [Pd(PPh_3)$_4$] yielded allene **10a** in only 4% yield, with mostly decomposition products (Table 8, entry 2). We next examined bases, which dramatically changed the outcome of the reaction. The addition of one equivalent of Cs_2CO_3 and 1 mol% [Pd(PPh_3)$_4$] led to allene formation in 87% yield, whereas Cs_2CO_3 alone exhibited no reactivity (Table 8, entries 3 and 4). Other palladium sources and phosphanes were examined (Table 8, entries 5–9) under the conditions given in entry 3 of Table 8. Both $Pd(OAc)_2$/2PPh_3 and [{Pd(allyl)Cl}$_2$]/4PPh_3 formed suitable catalysts for allene formation (73 and 80% yield; Table 8, entries 5 and 6, respectively). Some diene products (<5%) were also produced. The reaction with [{Pd(allyl)Cl}$_2$] and DPPE (4 equiv) did not reach completion within 1.5 hours (72 and 10% yield of **10a** and starting-material **1f**, respectively; Table 8, entry 7). Precatalyst [{Pd(allyl)Cl}$_2$]/PCy_3 (3 equiv) resulted in 93% yield (Table 8, entry 8). Finally, [{Pd(allyl)Cl}$_2$]/CyJohnPhos (3 equiv) and Cs_2CO_3 (1 equiv) at 60 °C resulted in 99% assay yield of the allene product **10a** (Table 8, entry 9). Screening the Buchwald phosphane ligands SPhos,

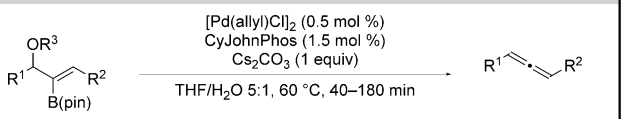
Table 8. Optimization of allene formation from 2-B(pin)-substituted allylic acetate **1 f**.

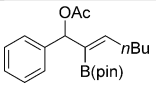
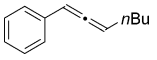
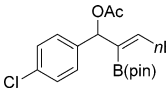
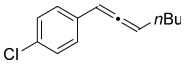
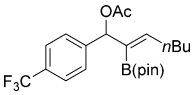
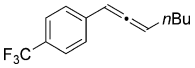
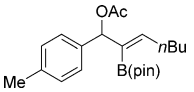
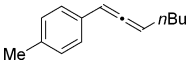
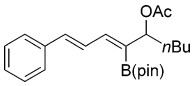
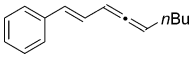
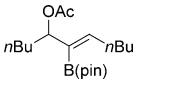
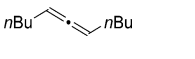
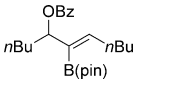
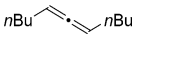
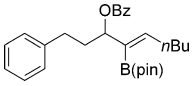
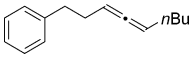
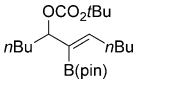
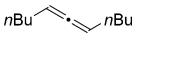
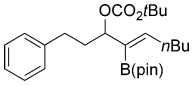
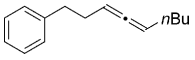


Entry	[Pd]	Ligand ([mol%])	Base ([equiv])	t [h]	Yield [%][b] 1 f[c]	10 a
1	$[Pd(PPh_3)_4]$	–	–	1.5	80	0
2	$[Pd(PPh_3)_4]$[d]	–	–	1.5	0	4
3	$[Pd(PPh_3)_4]$	–	Cs_2CO_3 (1)	1.5	0	87
4	–	–	Cs_2CO_3 (1)	1.5	95	<2
5	$Pd(OAc)_2$	PPh_3 (2)	Cs_2CO_3 (1)	1.5	0	73
6	$[\{Pd(allyl)Cl\}_2]$	PPh_3 (2)	Cs_2CO_3 (1)	1.5	0	80
7	$[\{Pd(allyl)Cl\}_2]$	DPPE (2)	Cs_2CO_3 (1)	1.5	12	72
8	$[\{Pd(allyl)Cl\}_2]$	PCy_3 (1.5)	Cs_2CO_3 (1)	1.0	0	93
9	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	$Cs_2CO_3$3 (1)	1.0	0	99
10	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	–	1.0	90	7
11	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	Cs_2CO_3 (0.5)	1.0	0	94
12	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	Cs_2CO_3 (3)	1.0	15	85
13	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	$NaOAc\cdot 3H_2O$ (3)	1.0	78	19
14	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	K_2CO_3 (3)	1.0	59	41
15	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	$NaHCO_3$ (3)	1.0	0	76
15	$[\{Pd(allyl)Cl\}_2]$	CyJohnPhos (1.5)	$NaHCO_3$ (1)	1.0	0	90

[a] Reactions were conducted at 0.17 M concentration on scale of 0.04 mmol. [b] Yield was determined by integration of the ^{1}H NMR spectra of the crude reaction mixture with 1,4-dimethoxybenzene as an internal standard. [c] Recovered **1 f**. [d] One equivalent of $[Pd(PPh_3)_4]$. CyJohnPhos = 2-(dicyclohexylphosphino)biphenyl.

Table 9. Allene formation from 2-B(pin)-substituted allylic acetates, benzoates, and carbonates.



Entry	Substrate		Product		Yield [%][a]
1		**1 f**		**10 a**	90
2		**1 i**		**10 b**	92
3		**1 h**		**10 c**	87
4		**1 k**		**10 d**	92
5		**1 m**		**10 e**	55
6		**1 a**		**10 f**	–[b]
7		**7 a**		**10 f**	53
8		**7 c**		**10 g**	79
9		**8 a**		**10 f**	85
10		**8 d**		**10 g**	83

[a] Yield of the isolated and purified products. [b] The starting material decomposed during the course of the reaction.

XPhos, DavePhos, and JohnPhos with $[\{Pd(allyl)Cl\}_2]$ resulted in slower conversion into allenes.[97] In the absence of Cs_2CO_3 at 60 °C, $[\{Pd(allyl)Cl\}_2]$/CyJohnPhos (3 equiv) resulted in the formation of only 7% of allene product **10 a** and 90% starting-material **1 f** (Table 8, entry 10). Lowering the Cs_2CO_3 loading to 0.5 equivalents did not affect the reactivity significantly (94% yield; Table 8, entry 11), and three equivalents of Cs_2CO_3 rendered the reaction slower (85 and 15% yield of **10 a** and starting-material **1 f**; Table 8, entry 12). Bases such as $NaOAc\cdot 3H_2O$, K_2CO_3, and $NaHCO_3$ were less effective (Table 8, entries 13–16). Ultimately, 0.5 mol% $[\{Pd(allyl)Cl\}_2]$, 1.5 mol% CyJohnPhos, and one equivalent of Cs_2CO_3 gave the best yield (Table 8, entry 9) of the conditions examined.

Substrate scope for allene formation from 2-B(pin)-substituted allylic acetates, benzoates, and carbonates

Subjecting various 1-aryl-2-B(pin)-3-butyl allylic acetates to the conditions given in entry 9 of Table 8 resulted in the formation of allene products. For example, aryl substrates bearing electron-withdrawing or electron-donating groups at the *para* position provided excellent yields of allene products **10 a**–**d** (87–92%; Table 9, entries 1–4). The styryl-derived allylic acetate **1 l** gave **10 e** in 55% yield without any noticeable isomerization of the vinyl group (Table 9, entry 5). Although 1,3-di-*n*-butyl-2-B(pin) allylic acetate **1 a** was not suitable for this transformation (Table 9, entry 6), benzoate substrates **7 a** and **7 c** were converted into allene products **10 f** and **10 g** in 53 and 79% yields, respectively, of the isolated products (Table 9, entries 7 and 8). With the dialkyl 2-B(pin)-substituted derivatives, the greater leaving-group ability of carbonates **8 a** and **8 d** resulted in higher yields of allene products **10 f** and **10 g** (85 and 83% yield; Table 9, entries 9 and 10). The results given in Tables 8 and 9 indicate that the proper choice of catalyst, substrates, and conditions enable the facile generation of allenes from 2-B(pin)-substituted allylic esters and carbonates.

Plausible catalytic cycle of the allene-formation reaction and allene racemization

To rationalize the formation of allylic substitution versus allene products, a plausible catalytic cycle for allene formation is illustrated in Figure 3. Electron-donating ligands, such as PCy_3 and CyJohnPhos, easily lead to π-allyl–palladium intermediates. In the presence of good nucleophiles, such as malonates or amines, allylic substitution occurs by addition of the nucleo-

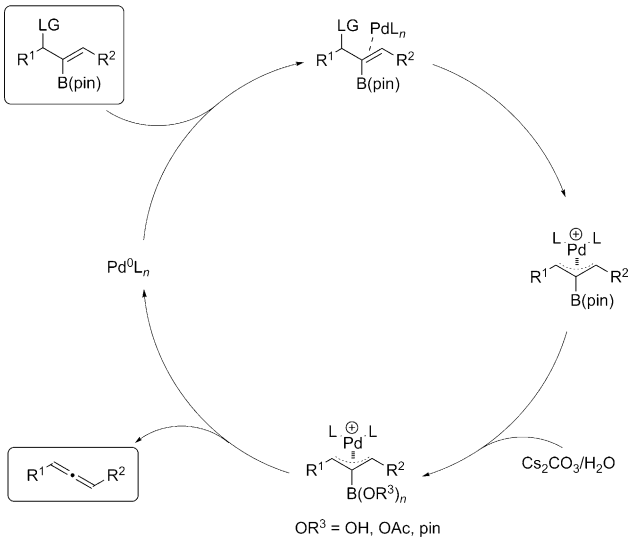
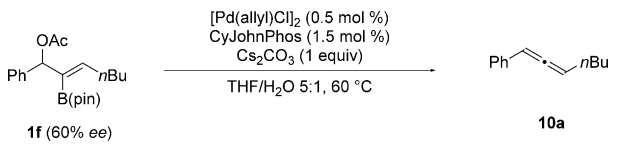


Figure 3. Plausible catalytic cycle for allene formation.

Table 10. Palladium-catalyzed allene-formation reaction of enantioenriched **1 f**.



1f (60% *ee*) **10a**

Entry	*t* [min]	Yield [%][a] **1 f**	**10 a**	*ee*[b] of **10 a** [%]
1	0	100	–	–
2	10	82	18	36
3	20	50	50	29
4	35	0	100	13
5	45	0	100	3
6	60	0	100	0

[a] The yield of conversion was determined by ^{1}H NMR spectroscopic analysis of aliquots of the unpurified reaction mixture. [b] Enantiomeric excess of allene **10 a** was determined by HPLC analysis (see the Supporting Information).

phile to the π-allyl–palladium species. In contrast, in the absence of a suitable nucleophile, the base is proposed to attack the empty coordination site on the boron atom or hydrolyze the boronate ester group. Several possible explanations for the observed dependency on base strength can be considered. The stronger bases are more likely to promote hydrolysis of the B(pin) group to a boronic acid group. Also, more reactive carbonate bases are harder and will be better nucleophiles toward the boron atom than either bicarbonate or acetate bases. Finally, elimination of a three-coordinate boron atom can be envisioned to lead to a palladium–allene π complex before allene dissociation.

Optically active allenes are ubiquitous intermediates and targets for the synthesis of natural products and biologically active compounds.[98,99] To investigate the possibility of chirality transfer in the catalytic cycle shown in Figure 3, we performed the allene-formation reaction with enantioenriched 2-B(pin)-allylic acetate **1 f** to generate allene product **10 a.** The reaction of **1 f** (60% *ee*) in the presence of the Pd/CyJohnPhos catalyst afforded the enantioenriched allene **10 a** with 36% *ee* in 18% yield in 10 minutes (Table 10, entry 2). When the reaction reached completion within 35 minutes, however, a significant loss of enantiometic excess was observed (Table 10, entries 3 and 4). Finally, allene product **10 a** was racemized completely within one hour (Table 10, entry 6). It is noteworthy that B(pin)-substituted **1 f** (60% *ee*) was not racemized during the course of the reaction. These results suggest that 2-B(pin)-allylic acetate undergoes stereoselective allene formation, however, a competing racemization of the allene product in the presence of the palladium catalyst, probably through hydropalladation, is responsible for the observed loss of enantiomeric excess over time.[100,101]

Conclusion

The application of multicomponent tandem reactions to molecules bearing more than one reaction site is a powerful synthetic strategy for the rapid generation of molecular complexity and diversity. The key to the development of such a methodology is to tailor the catalyst, reagents, and conditions to afford chemoselective activation of the substrate. Toward this goal, we have introduced a new class of bifunctional reagents that contains vinyl boronate esters embedded within allylic acetates. The requisite 2-B(pin)-substituted allylic acetates were synthesized on a gram scale in one-pot procedures from readily available materials by using the heterobimetallic chemistry developed in our laboratory.[15–18]

To facilitate applications of our bifunctional substrates, methods to control the chemoselectivity of their activation is crucial. The challenge is to employ common palladium–phosphane-based catalysts and modulate their activation of 2-B(pin)-substituted allylic acetates through manipulation of the reagents, substrates, and conditions. In the case of allylic substitutions, the reactions were conducted under conditions in which the B(pin) group was stable to hydrolyze (and palladium hydroxide intermediates are not likely to be formed),[13,102] thus inhibiting B to Pd transmetalation. Under such conditions, oxidative ionization of the acetate and nucleophilic addition to the π-allyl–palladium intermediate were much faster than transmetalation. In the Suzuki–Miyaura cross-coupling reaction of 2-B(pin)-substituted allylic acetates, the chemoselectivity of the Pd^0 center is on the order of Ar-I > Ar-Br > allylic acetate. Once the Pd^0 center is converted into Pd^{II} by the aryl halide, ionization of the allylic acetate does not interfere with the cross-coupling reaction. Under conditions in which the B(pin) group hydrolyzes to the boronic acid (or palladium hydroxides can form), transmetalation is also fast. Detailed study of this system indicates the relative order of reactivity toward the Pd^0 center is Ar-I > Ar-Br > allylic carbonate > allylic benzoate > allylic acetate, with the reactivity of the allylic carbonates approaching that of aryl bromides. For allylic acetates with the acetate group in benzylic position, the allylic acetate is more reactive than aryl bromides in the presence of L_2Pd. The observations outlined herein enabled a complete reversal of chemo-

selectivity from allylic substitution reactions to Suzuki–Miyaura cross-coupling of allylic acetates, benzoates, and carbonates.

In the case of the third reaction manifold, namely, allene formation, oxidative ionization of the allylic acetate occurs to generate the π-allyl–palladium intermediate. In the absence of a nucleophile, we hypothesized that hard bases (i.e., CO_3^{2-}, HCO_3^-, and AcO^-), or the hydroxide ion generated from these reagents, attack the unsaturated boron atom to make ate complexes that can undergo elimination of a three-coordinate boron atom and to generate an intermediate Pd(η^2-allene). The rate of allene formation is base dependent, with the more-basic carbonate ion more reactive than the less-basic acetate species. Our method provides high yields of 1,3-disubstituted allenes under mild conditions. Although the allene formation reaction of enantioenriched 2-B(pin) allylic acetate provided the enantioenriched allene product, palladium-catalyzed racemization of the allene resulted in the racemic product over time.

With the ability to control chemoselectivity, various tandem reactions were investigated. The allylic substitution of 2-B(pin)-substituted allylic acetates can be followed with a Suzuki–Miyaura cross-coupling reaction to afford *E*-trisubstituted allylic amines and malonates with four points of diversity. Enantioenriched 2-B(pin)-substituted allylic acetates undergo allylic substitution with net stereochemical retention, thus allowing isolation of B(pin)-containing substitution products or α-amino ketones with little or no loss of enantiomeric excess. Alternatively, the allylic substitution of 2-B(pin)-substituted allylic acetates can be paired with the oxidation of vinyl boronates to provide valuable α-amino ketones and 1,4-dicarbonyl compounds.

Given the high levels of control over the chemoselectivity in our optimized palladium-catalyzed reactions of 2-B(pin)-substituted allylic acetate derivatives, we are optimistic that these bifunctional substrates will serve as useful intermediates in synthesis.

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Keywords: allenes · allylic substitution · chemoselectivity · cross-coupling · palladium

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