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Allylic Substitution vs. Suzuki Cross-Coupling: Capitalizing on Chemoselectivity with Bifunctional Substrates**

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Abstract

One catalyst, two reactions; a tale of chemoselectivity: Given the choice between an allylic acetate and a vinylboronate ester, palladium preferentially reacts with the allylic acetate giving the allylic substitution product. In the presence of an aryl bromide and base, Suzuki cross-coupling subsequently ensues to afford allylic amines.

Keywords

Chemoselectivity; Bifunctional substrates; Tandem reactions; Allylic Substitution; Suzuki cross-coupling

The greatest challenge in complex molecule synthesis has been, and continues to be, chemoselectivity.[1-3] Highly chemoselective reactions obviate the need for elaborate protecting group strategies and maximize synthetic efficiency. To achieve high levels of chemoselectivity, chemists are increasingly employing transition metal catalysts, with palladium being favored.[4,5] Two of the most important and frequently applied palladium-catalyzed reactions are the Suzuki cross-coupling[6,7] and the Tsuji-Trost allylic substitution.[4,8-10] We envisaged, therefore, that bifunctional reagents possessing both allylic acetates and a vinylboronate esters would combine the utility of these powerful reactions. The possibility of employing such reagents, however, hinges on chemoselectivity, because both the Suzuki and the Tsuji-Trost reactions are catalyzed by palladium phosphine complexes. In this study, we have embedded vinylboronates ester *within allylic acetates*. We disclose the chemoselective reactions of B(pin)-substituted allylic acetates in tandem allylic

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substitution/Suzuki cross-coupling and allylic substitution/oxidations to provide rapid access to valuable trisubstituted allylic amines, 1,4-dicarbonyl compounds, and α -amino ketones.

For any synthetic method to be useful, the substrates must be readily accessible. The B(pin) allylic acetates were prepared in one-pot using our stereodefined 1-alkenyl-1,1-heterobimetallic reagents (Table 1).[11,12] Thus, hydroboration of air stable alkynyldioxaborolanes with dicyclohexylborane and selective B to Zn transmetalation of the vinyl-BCy₂ moiety generates the heterobimetallic intermediate. Addition of the Zn-C bond to aldehydes and quenching the resulting alkoxides with acetic anhydride provides (*E*)-allylic acetates **1a-1g** in 52–85% yield (Table 1). To demonstrate scalability, **1a-1c** were prepared in gram quantities.

At the outset of our investigation with B(pin) allylic acetates, we were concerned about the chemoselective activation of the allylic acetate vs. transmetalation of the B-C bond, which is a key step in Suzuki cross-coupling[6] and base-free oxidative Heck reactions.[13,14] A second concern was that the bulky B(pin) group would retard or inhibit oxidative ionization of the allylic acetate by the Pd(0) catalyst. 2-Substituted allylic acetates and halides exhibit decreased reactivity.[15,16]

Subjecting the di-*n*-Bu derived 2-B(pin) allylic acetate (**1a**) to various palladium sources with either NaCH(CO₂Me)₂ or morpholine indicated that [ClPd(allyl)]₂ and PPh₃ formed a suitable catalyst (see SI for details). When **1a** was combined with [ClPd(allyl)]₂ (5 mol %), PPh₃ (20 mol %), and NaCH(CO₂Me)₂ in THF, the allylic substitution product was obtained in 81% yield after 10 h at 40 °C (entry 1, Table 2). Importantly, the vinyl boronate ester remained intact.

Employing similar conditions, secondary amines participated in the allylic substitution to provide B(pin)-substituted allylic amines in 79–83% yield (entries 2–4). The primary amine, benzyl amine, also underwent allylic substitution (65% yield, entry 5). Use of B(pin) allylic acetates **1b** and **1c** with NaCH(CO₂Me)₂ or morpholine gave unexpected regioselectivity ($\geq 10:1$) derived from attack at the *benzylic* position in 45–79% yield (entries 6–9). B(pin) allyl acetate **1c** was less reactive than **1b** in allylic substitutions. The reactions work well with electron withdrawing or electron donating substituents on the aryl group (**1d-1f**, $>12:1$ regioselectivity, entries 10–13). The dialkyl substrate **1g** underwent nucleophilic attack at the less hindered position with $>20:1$ regioselectivity (entry 14).

Regioselectivity in the allylic substitution can be affected by the nature of the ligands and nucleophile.[5] A comparison of the reactivity and regioselectivity of B(pin)-substituted allylic acetates with the parent and 2-methyl derivatives was therefore performed (Scheme 1). In contrast to attack at the *benzylic* position in Table 2, the parent compound (R=H) underwent allylic substitution with attack distal to the aryl with high regioselectivity (9:1). No reaction occurred with the 2-methyl substrate under our conditions. The regioselectivities and reactivities in Scheme 1 highlight important distinctions between the B(pin)-substituted allylic acetates and the parent and methyl substituted derivatives.

To develop the full potential of our bifunctional substrates, we performed tandem processes beginning with allylic substitution followed by reactions of the vinyl boronate ester.[17] As illustrated in Table 3, the palladium-catalyzed allylic substitution was performed as in Table 2. The reaction mixture was then treated with alkaline hydrogen peroxide to oxidize the vinyl boronate ester. The resulting α -amino ketones were isolated in 65–85% yield in this one-pot procedure (Table 3, entries 1–5). A milder oxidation with NaBO₃·H₂O resulted in an increased yield (entry 6 vs. 5). It is noteworthy that such products would not be easily prepared by standard π -allyl chemistry. Trost has shown that alkoxy-bearing allylic acetates

provide enol ethers, which participate in allylic substitutions. The resulting enol ether products can be hydrolyzed to ketones.[18]

The observation that palladium-catalyzed allylic substitutions can be conducted without interference by the B(pin) substituent hints at the possibility of achieving a one-pot allylic substitution/Suzuki cross-coupling reaction. Ideally both steps can be catalyzed using the same palladium source. A successful allylic substitution/cross-coupling sequence would, therefore, make possible the synthesis of a variety of 2-arylated allylic amines from (Bpin) substituted allylic acetates (**1**), amines, and aryl bromides. Thus, after the completion of the allylic substitution with morpholine, the reaction mixture was diluted with THF/water, Cs₂CO₃ and aryl bromide were added, and the mixture heated to 75 °C (Scheme 2). After workup, arylated trisubstituted allylic amines were isolated in 52–70% yields. Importantly, only the (*E*)-double bond isomer was observed.

Enantioenriched allylic amines are important intermediates and are found in natural products.[19] With this in mind, we conducted the allylic substitution with **1b** of 80% ee and morpholine to generate the 2-B(pin)-substituted benzyl amine **2b** in 82% yield without loss of ee (Scheme 3).[20] The one-pot allylic substitution/B–C bond oxidation with NaBO₃·H₂O furnished the α -amino ketone with 77% ee in 80% yield.

In summary, scalable one-pot syntheses of 2-B(pin)-substituted allylic acetates **1a–1g** are reported. These bifunctional templates are excellent substrates for chemoselective Pd-catalyzed allylic substitutions, despite the well-known propensity of Pd(II) to react with B–C bonds. It is noteworthy that these reactions proceed via boron-substituted π -allyl palladium intermediates, which have been underutilized in allylic substitutions[21,22] and related reactions.[23–25] Additionally, the regioselectivity in the allylic substitution is opposite that observed with the parent allylic acetate.

The allylic substitution can be paired with oxidation to provide valuable α -amino ketones and 1,4-dicarbonyl compounds, which are not accessible by the Tsuji-Trost allylation alone. The allylic substitution can be followed with a Suzuki cross-coupling to afford (*E*)-trisubstituted allylic amines with four points of diversity. The key to success of this, and other processes,[26–33] is the remarkable chemoselectivities exhibited by palladium-based catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Probing Regioselectivity with 2-Substituted Allylic Acetates.

Scheme 2.
Tandem Allylic Substitution/Suzuki Cross-Coupling.

Scheme 3. Allylic Substitution of Enantioenriched B(pin)-Substituted Allylic Acetate **1b**.

Table 1One-pot Synthesis of B(pin)-Substituted Allylic Acetates.^[a]

$ \begin{array}{c} \text{B(pin)} \\ \\ \text{R} \end{array} \xrightarrow[\text{ii. Me}_2\text{Zn}]{\text{i. Cy}_2\text{BH}} \left[\text{MeZn} \begin{array}{c} \text{CH} \\ \\ \text{B(pin)} \end{array} \text{CH} \text{R} \right] \xrightarrow[\text{iv. Ac}_2\text{O}]{\text{iii. R'CHO}} \begin{array}{c} \text{OAc} \\ \\ \text{R'} \end{array} \text{CH} \begin{array}{c} \text{CH} \\ \\ \text{B(pin)} \end{array} \text{R} $				
entry	R	R'	Compound	Yield [%] ^[b]
1	<i>n</i> Bu	<i>n</i> Bu	1a	82
2	Ph	<i>n</i> Bu	1b	75
3	<i>n</i> Bu	Ph	1c	67
4	4-C ₆ H ₄ -F	<i>n</i> Bu	1d	73
5	4-C ₆ H ₄ -CF ₃	<i>n</i> Bu	1e	78
6	4-C ₆ H ₄ -OMe	<i>n</i> Bu	1f	52
7	<i>c</i> Hex	<i>n</i> Bu	1g	85

^[a] See Supporting Information for details.^[b] Yield of isolated and purified products.

Product	Yield [%] ^[b]
<p>Chemical structure of the product: $n-Bu-CH(CH_3)-CH=CH-nBu$, where $B(pin)$ is attached to the terminal carbon of the double bond.</p>	81 ^[c]

$\xrightarrow[\text{mol \%}]{\text{I}_2 \text{ (5 mol \%)[c]}}$
 $\xrightarrow[\text{mol \%}]{\text{(10 mol \%)[c]}}$
 ; 10–24 h

Product	Yield [%][b]
	83[c]

I_2 (5 mol %)^[c]
(10 mol %)^[c]
mol %
; 10–24 h

Yield [%] ^[b]	Product
80/ ^[c]

I_2 (5 mol %)[c]
(10 mol %)[c]
mol %
; 10–24 h

Yield [%][b]
79[c]

Product

65[c]

I_2 (5 mol %)[c]
 (10 mol %)[c]
 mol %
 ; 10–24 h

Yield [%][b]

80[d,f]

45[d,e]

Product

I_2 (5 mol %)^[c]
 (10 mol %)^[c]
 mol %
 ; 10–24 h

Yield [%] ^[b]	Product
79 ^[c,f]	<p>Chemical structure of the product: $CH(CO_2Me)_2-CH(Ph)-CH=CH-nBu$, where $B(pin)$ is attached to the terminal carbon nBu.</p>
51 ^[c,f]

I_2 (5 mol %)[c]
(10 mol %)[c]
mol %
; 10–24 h

Yield [%][b]
75[d,f]

Product

I_2 (5 mol %)[c]
(10 mol %)[c]
mol %
; 10–24 h

Yield [%][b]

Product

90[d,f,g]

I_2 (5 mol %)^[c]
 (10 mol %)^[c]
 mol %
 ; 10–24 h

Product	Yield [%] ^[b]
<p> $p\text{-CF}_3\text{-C}_6\text{H}_4$ $\text{CH}(\text{CO}_2\text{Me})_2$ $n\text{Bu}$ $\text{B}(\text{pin})$ </p>	92 ^[d,f,g]

Product	Yield [%] ^[b]
	80 ^[d,f,g]

I_2 (5 mol %)^[c]
 (10 mol %)^[c]
 mol %
 ; 10–24 h

Yield [%]^[b]
 60^[c]

Product

[a] See the Supporting Information for experimental details.

[b] Yield of isolated and purified products.

[c] $[\text{Pd}(\text{allyl})\text{Cl}]_2$.

[d] $\text{Pd}(\text{OAc})_2$.

[e] 30% SM recovered.

[f] Regioselectivity $\geq 10:1$.

[g] BSA and catalytic KOAc used.

Table 3One-pot Synthesis of α -Substituted Ketones.

Entry	Nu [−] /NuH	Allyl Acetate	Yield [%]/
1	$\text{NaCH}(\text{CO}_2\text{Me})_2$	1a	85
2		1a	82
3	PhCH_2NHMe	1a	81

Entry	Nu ⁻ /NuH	Allyl Acetate	Yield [%]
4		1a	75

Entry	Nu ⁻ /NuH	Allyl Acetate	Yield [%] ^[a]
5		1b	65
6		1b	78 ^[b,c]

^[a]Yield of purified and isolated material.

^[b]Allylation conducted with Pd(OAc)₂ (5 mol %) and PPh₃ (10 mol %) at RT.

^[c]Oxidation done with 3 equiv of NaBO₃·H₂O in THF/H₂O (1:1) at RT.