Chemoselectivity

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

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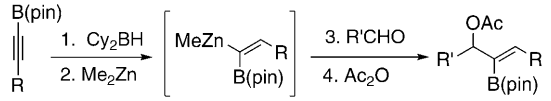
In memory of Keith Fagnou

The greatest challenge in the synthesis of complex molecules 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 that possess both allylic acetate and a vinylboronate ester groups 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 vinylboronate ester moieties within allylic acetate derivatives. Herein, we disclose the chemoselective reactions of B(pin)-substituted allylic acetates in tandem allylic substitution/Suzuki cross-coupling and allylic substitution/oxidation reactions 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)-substituted 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–BCy_2 moiety generates the heterobimetallic intermediate. Addition of the Zn–C bond to aldehydes and quenching the resulting alkoxides with acetic anhydride provided (*E*)-allylic acetates **1a**–**1g** in 52–85% yield (Table 1). To demonstrate the scalability of the reaction, **1a**–**1c** were prepare in gram quantities.

At the outset of our investigation with B(pin)-substituted allylic acetates, we were concerned about the chemoselective activation of the allylic acetate versus 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. It is known that 2-substituted allylic acetates and allylic halides exhibit decreased reactivity.[15,16]

Table 1: One-pot synthesis of B(pin)-substituted allylic acetates.[a]



Entry	R	R′	Product	Yield [%][b]
1	*n*Bu	*n*Bu	**1a**	82
2	Ph	*n*Bu	**1b**	75
3	*n*Bu	Ph	**1c**	67
4	4-FC_6H_4	*n*Bu	**1d**	73
5	4-$CF_3C_6H_4$	*n*Bu	**1e**	78
6	4-$OMeC_6H_4$	*n*Bu	**1f**	52
7	Cy	*n*Bu	**1g**	85

[a] See the Supporting Information for details. [b] Yield of isolated and purified product. Cy = cyclohexyl, pin = pinacol.

Subjecting the bis(*n*-butyl) allylic acetate (**1a**) to various palladium sources with either $NaCH(CO_2Me)_2$ or morpholine indicated that $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$ and PPh_3 formed a suitable catalyst (see the Supporting Information for details). When **1a** was combined with $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$ (5 mol%), PPh_3 (20 mol%), and $NaCH(CO_2Me)_2$ in THF, the allylic substitution product was obtained in 81% yield after 10 h at 40 °C (Table 2, entry 1). Importantly, the vinyl boronate ester group remained intact.

By employing similar reaction conditions, secondary amines participated in the allylic substitution and provided B(pin)-substituted allylic amines in 79–83% yield (Table 2, entries 2–4). The primary amine, benzyl amine, also underwent allylic substitution (65% yield; Table 2, entry 5). The reaction of B(pin)-substituted allylic acetates **1b** and **1c** with $NaCH(CO_2Me)_2$ or morpholine gave unexpected regioselectivity (≥10:1) derived from attack at the benzylic position (45–80% yield; Table 2, entries 6–9). Compound **1c** was less reactive than **1b** in the allylic substitution reaction. The reactions worked well with electron-withdrawing or electron-donating substituents on the aryl group (**1d**–**1f**, >12:1 regioselectivity; Table 2, entries 10–13). The dialkyl substrate **1g** underwent nucleophillic attack at the less hindered position with >20:1 regioselectivity (Table 2, entry 14).

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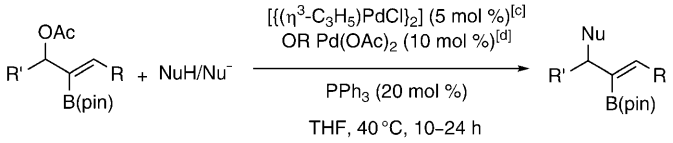
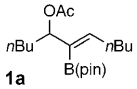
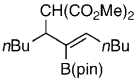
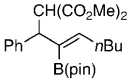
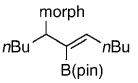
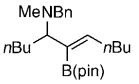
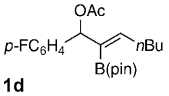
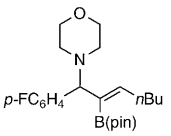
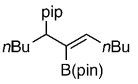
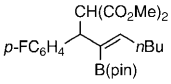
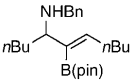
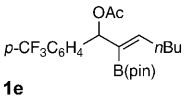
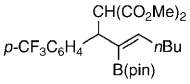
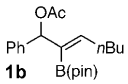
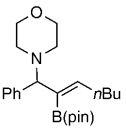
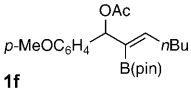
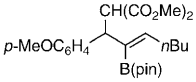
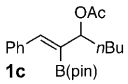
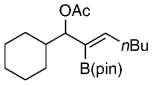
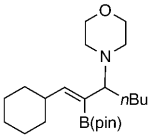
Table 2: Palladium-catalyzed allylic substitution with B(pin)-substituted allylic acetates.[a]

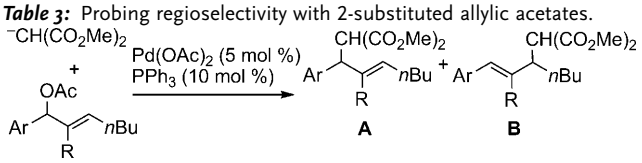


Entry	Allylic acetate	Nucleophile	Product	Yield [%][b]	Entry	Allylic acetate	Nucleophile	Product	Yield [%][b]
1	 **1a**	$NaCH(CO_2Me)_2$		81[c]	8	**1b**	$NaCH(CO_2Me)_2$		79[c,f]
2	**1a**			83[c]	9	**1c**	$NaCH(CO_2Me)_2$		51[c,f]
3	**1a**	BnNHMe		80[c]	10	 **1d**			75[d,f]
4	**1a**			79[c]	11	**1d**	$CH_2(CO_2Me)_2$		90[d,f,g]
5	**1a**	$BnNH_2$		65[c]	12	 **1e**	$CH_2(CO_2Me)_2$		92[d,f,g]
6	 **1b**			80[d,f]	13	 **1f**	$CH_2(CO_2Me)_2$		80[d,f,g]
7	 **1c**			45[d,e]	14	 **1g**			60[c,f]

[a] See the Supporting Information for experimental details. [b] Yield of isolated and purified products. [c] $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$. [d] $Pd(OAc)_2$. [e] 30% of unchanged starting material was recovered. [f] Regioselectivity of $\geq$10:1. [g] *N*,*O*-Bis(trimethylsilyl)acetamide (BSA) and catalytic KOAc were used. Bn = benzyl, morph = morpholine, pip = piperidine THF = tetrahydrofuran.

Regioselectivity in the allylic substitution reaction 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 (Table 3). In contrast to attack at the benzylic position as shown in Table 2, the parent compound (R = H; Table 3, entry 1) underwent allylic substitution with attack distal to the aryl group with high regioselectivity (9:1). No reaction occurred with the 2-methyl substrate under our reaction conditions (Table 3, entry 4). The regioselectivities and reactivities shown in Table 3 highlight important distinctions between the B(pin)-substituted allylic acetates and the parent and methyl-substituted derivatives.

Table 3: Probing regioselectivity with 2-substituted allylic acetates.

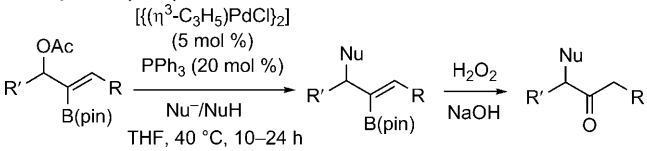


Entry	Ar	R	**A**/**B**	Yield [%][a]
1	Ph	H	1:9	85
2	Ph	B(pin)	>10:1	79
3	4-$CF_3C_6H_4$	B(pin)	20:1	92
4	Ph	CH_3	–	n.r.

n.r. = no reaction.

To develop the full potential of our bifunctional substrates, we performed tandem processes beginning with allylic substitution and subsequent reactions of the vinyl boronate ester.[17] As illustrated in Table 4, 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 4, entries 1–5). A milder oxidation with $NaBO_3 \cdot H_2O$ resulted in an increased yield (compare Table 4, entries 5 and 6). Notably, such products are not easily prepared by standard π-allyl chemistry. Trost and Gowland

Table 4: One-pot synthesis of α-substituted ketones.



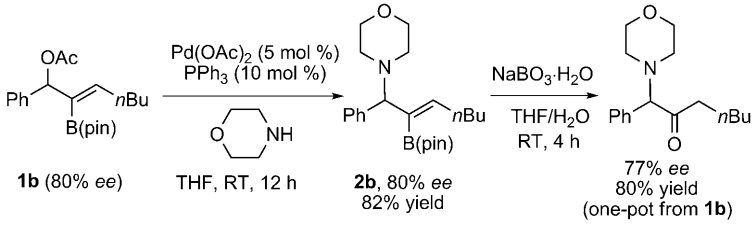
Entry	Nu^-/NuH	Allylic acetate	Yield [%][a]
1	$NaCH(CO_2Me)_2$	**1a**	85
2		**1a**	82
3	$PhCH_2NHMe$	**1a**	81
4		**1a**	75
5		**1b**	65
6		**1b**	78[b,c]

[a] Yield of purified and isolated product. [b] Allylation carried out with $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) at RT. [c] Oxidation carried out with 3 equivalents of $NaBO_3{\cdot}H_2O$ in THF/H_2O (1:1) at RT.

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 B(pin)-substituted benzyl amine **2b** in 82% yield without loss in enantiomeric excess (Scheme 2).[20] The one-pot allylic substitution/B–C bond oxidation with $NaBO_3{\cdot}H_2O$ furnished the α-amino ketone with 77% *ee* in 80% yield.

In summary, scalable one-pot syntheses of B(pin)-substituted allylic acetates **1a–1g** are reported. These bifunctional templates are excellent substrates for chemoselective palladium-catalyzed allylic substitution reactions, despite the well-known propensity of Pd^{II} to react with B–C bonds. Notably, 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 to that observed with the parent allylic acetate.

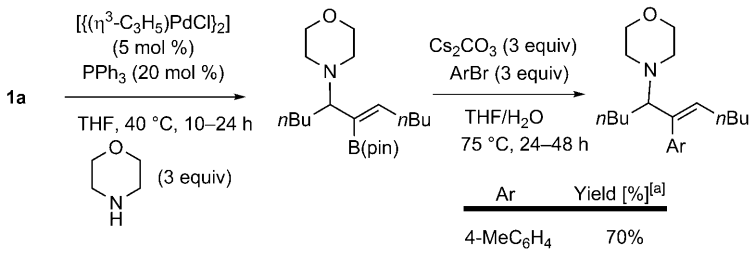
The allylic substitution can be paired with oxidation to provide valuable α-amino ketones and 1,4-dicarbonyl compounds, which are not accessible by the Tsuji–Trost allylation alone. The allylic substitution can be followed by Suzuki cross-coupling to afford *E*-trisubstituted allylic amines with four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



Scheme 2. Allylic substitution of enantioenriched B(pin)-substituted allylic acetate **1b**.

have shown that allylic acetates bearing a 2-alkoxy group undergo allylic substitution reactions to generate enol ethers. 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 B(pin)-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 (10:1), Cs_2CO_3 and aryl bromide were added, and the reaction mixture was heated to 75 °C (Scheme 1). After workup, arylated trisubstituted allylic amine derivatives were isolated in 52–70% yield. Importantly, only the *E* double-bond isomer was observed.



Ar	Yield [%][a]
$4\text{-}MeC_6H_4$	70%
$4\text{-}OMeC_6H_4$	65%
$3\text{-}NC_5H_3$	52%

Scheme 1. Tandem allylic substitution/Suzuki cross-coupling. [a] Yield of isolated and purified product.

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