

An evaluation of palladium-based catalysts for the base-free borylation of alkenyl carboxylates

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Synthesis of organoboron derivatives is a key application of catalytic cross-coupling, with the Pd-catalyzed Miyaura borylation among the most versatile methods available. We have evaluated several Pd-based systems for borylation of alkenyl acetates and pivalates, with the optimal system heavily dependant on the substrate structure.

Boron-based functional groups serve as versatile synthetic handles in many metal-catalyzed cross-coupling reactions.^{1,2} As the Suzuki-Miyaura coupling has increased in importance over recent decades, so has the need for reactions that install the necessary boron-based functional groups.³ Following seminal work in this area by Miyaura,⁴ Pd-catalyzed borylation of halide or triflate electrophiles, typically with B₂pin₂ as the boron source and driven by the addition of a weak base, remains one of the most widely-used methods.⁵ Although there are numerous recent studies on improving this general reaction,^{6,7} there remains a reliance on (pseudo)halide leaving groups, particularly bromides and triflates.

An alternative approach that can improve reaction mass efficiency and use new feedstocks/building blocks is the substitution of oxygen-based leaving groups via C–O activation.^{8–12} Unfortunately, the requisite C–O activation is difficult, leading to few systems reported for C–O borylation using Rh,^{13,14} Ni,^{15–18} and more recently Fe^{19,20} (Figure 1a). Among the possible O-based electrophiles, aryl and alkenyl carboxylates offer several advantages, including ease of installation and base-free reaction conditions;^{21,22} however, there is only one report of successful borylation with this class of substrate using Rh catalysis.¹³ Recent work from our research group has shown that Pd(0) can undergo C–O oxidative addition with heteroaryl and alkenyl carboxylates, and that Pd-catalyzed cross-coupling of alkenyl acetate and pivalate electrophiles with aryl boronic acids is possible under base-free conditions (Figure 1b).^{21,23,24} Here, we extend this reactivity to Pd-catalyzed borylation by evaluating three distinct catalytic systems using Pd(0) and Pd(II) precursors (Figure 1c).

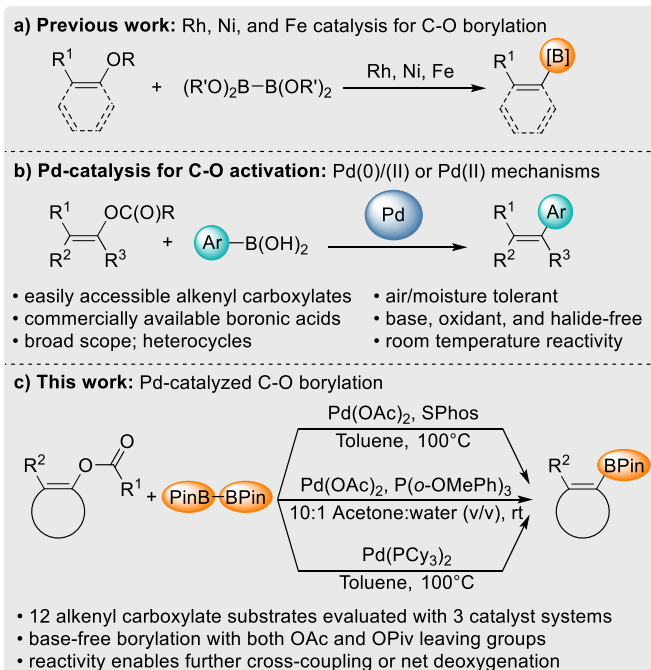
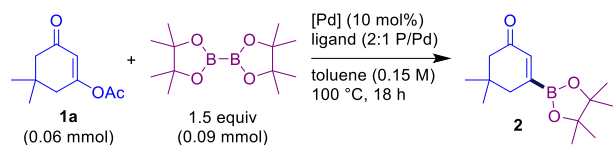


Fig. 1 a) Prior catalytic approaches to C–O borylation; b) C–O activation in C–C bond formation with arylboronic acids; c) an evaluation of catalytic systems for borylation involving C–O activation

Prior screening on the Pd-catalyzed Suzuki coupling of alkenyl carboxylates revealed two suitable catalytic systems. One involves a mixture of Pd(OAc)₂ and tris(*ortho*-methoxyphenyl)phosphine to generate an active system *in situ*. This catalyst operates at room temperature under air and in the presence of water, likely through a Pd(II)-mediated mechanism.^{24–26} The second is Pd(PCy₃)₂, a single-component Pd(0) catalyst that is capable of C–O oxidative addition at elevated temperatures.²³ To determine if other Pd/ligand combinations could be active for borylation catalysis under base-free conditions, we conducted targeted microscale high-throughput screening of the reaction between B₂pin₂ and dimedone-derived alkenyl acetate **1a** (Figure 2).



Ligand	$\text{Pd}(\text{OAc})_2$	$\text{Pd} \cdot \text{dba} \cdot \text{CHCl}_3$	$[\text{Pd}(\text{acetanilide})\text{OAc}]_2$	$\text{DMP} \cdot \text{DAB} \cdot \text{Pd} \cdot \text{MAH}$	
$\text{P}(\text{o-OMePh})_3$	41	41	70	22	% Conv. 1a
	28	23	50	4	% Yield 2
dppf	40	15	54	12	% Conv. 1a
	11	0	19	9	% Yield 2
XPhos	68	15	46	22	% Conv. 1a
	30	2	5	4	% Yield 2
SPhos	78	12	26	13	% Conv. 1a
	62	1	7	4	% Yield 2
No Ligand	9	4	18	8	% Conv. 1a
	4	2	3	0	% Yield 2

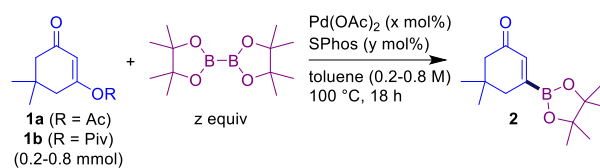
	$\text{Pd}(\text{PCy}_3)_2$	$(\text{dppf})\text{PdCl}_2 \cdot \text{DCM}$	No Pd	No Pd or B_2Pin_2	
No Ligand	98	11	5	5	% Conv. 1a
	62	4	0	0	% Yield 2

Fig. 2 Catalyst screening for the borylation of **1a**. Conversion and yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Initially we evaluated the efficacy of four ligands, including the previously identified $\text{P}(\text{o-OMePh})_3$ and three effective cross-coupling ligands in dppf, XPhos, and SPhos. These were paired with four palladium sources: two Pd^0 compounds including the recently reported $\text{DMP} \cdot \text{DAB} \cdot \text{Pd} \cdot \text{MAH}$,²⁷ and two Pd^{II} compounds. In addition, we evaluated two single-component precatalysts: $\text{Pd}(\text{PCy}_3)_2$ and $(\text{dppf})\text{PdCl}_2$. Several combinations enabled borylation to occur, with Pd^{II} sources generally outperforming Pd^0 . Control experiments in the absence of ligand resulted in little to no product formation, and further control experiments with no Pd and with no Pd or B_2pin_2 resulted in little/no conversion of **1a**. We identified the combination of $\text{Pd}(\text{OAc})_2$ and SPhos as the most active *in situ* candidate (78% conversion and 62% solution yield) for further optimization. $\text{Pd}(\text{PCy}_3)_2$ is also effective, with a similar solution yield (62%) though poorer mass balance.

Using the $\text{Pd}(\text{OAc})_2/\text{SPhos}$ system as a starting point, a full factorial multivariate screen was designed to rapidly identify an optimal system (Figure 3). In addition to providing an improved, optimized set of conditions, this screen also offered additional insights into the catalytic system. Excess (3.0 equiv) SPhos reduced catalytic efficiency with both 4.0 and 10.0 mol% $\text{Pd}(\text{OAc})_2$, consistent with a monophosphine-Pd active catalyst.

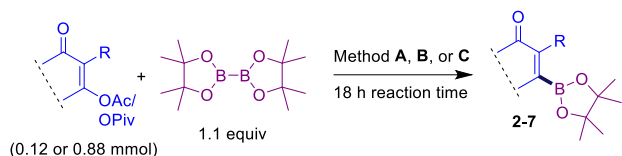
In all cases, **1a** conversion and yield of **2** is improved with a large excess of B_2Pin_2 . Using this excess generally increases the yield more than the conversion, leading to better overall mass balance. With 0.2M of **1a**, 10 mol% $\text{Pd}(\text{OAc})_2$, 15 mol% SPhos and 2.0 equivalents of B_2Pin_2 an optimal yield was obtained.



Substrate	[1] (M)	$\text{Pd}(\text{OAc})_2$ loading (mol%)	SPhos equiv per Pd	B_2Pin_2 equiv	% Conv. 1	% Yield 2	
1a	0.2	4.0	1.5	1.1	29	11	Centerpoint
			2.0	2.0	40	25	
			3.0	1.1	30	1	
		7.5	1.5	1.5	58	33	Maximum
			1.5	2.0	89	71	
			2.0	1.1	74	44	
	0.8	10.0	1.5	2.0	92	62	
			2.0	2.0	100	72	
1a	0.2	10.0	1.5	2.0	89	71	TON = 7
	0.4	5.0			100	67	TON = 13
	0.6	3.3			100	58	TON = 18
	0.8	2.5			100	44	TON = 18
1b	0.8	2.5	1.5	2.0	100	72	TON = 29

Fig. 3 Multivariate optimization of the borylation of **1a**. Conversion and yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

While this set of conditions provides good solution yield of **2**, it gives a very modest TON of 7; therefore, we sought to improve catalytic efficiency by increasing the substrate:catalyst ratio. From the full factorial screen, simply reducing Pd concentration has a deleterious effect on yield. Keeping the palladium and ligand concentration constant, we evaluated increasing substrate concentration from $[\mathbf{1a}] = 0.2$ M to 0.8 M, with a concomitant decrease in the substrate:catalyst mol ratio from 10 mol% Pd to 2.5 mol% Pd. This does lead to increased TON; however, it also results in poorer mass balance, with the chemical yield of **2** being reduced to only 44% at $[\mathbf{1a}] = 0.8$ M. We attributed this to competitive decomposition of **1a** (e.g. by hydrolysis). To impede substrate decomposition, we assessed the more sterically-hindered and electron-rich pivalate derivative **1b** at a concentration of 0.8 M. This results in significantly better mass balance and higher catalyst TON, with a 72% solution yield of **2**.



Method A: Pd(OAc)₂ (4 mol%) / P(o-OMePh)₃ (6 mol%), acetone/water (10:1, 0.6 M), rt
 Method B: Pd(OAc)₂ (2.5 mol%) / SPhos (3.8 mol%), toluene (0.8 M), 100 °C
 Method C: Pd(PCy₃)₂ (10 mol%), toluene (0.2 M), 100 °C

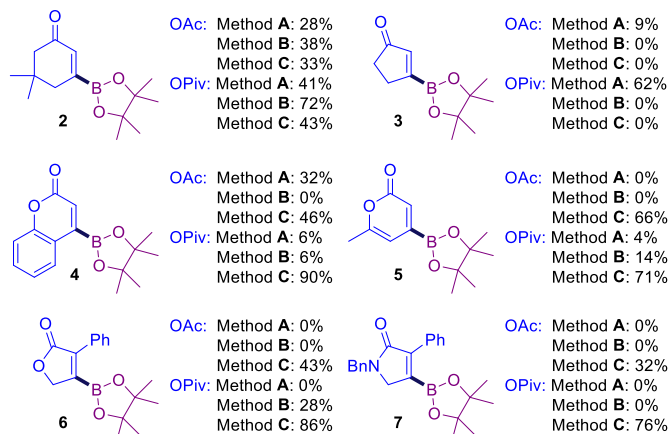


Fig. 4 Comparison of Pd-catalyzed methods for the borylation of alkenyl acetate and pivalate substrates. Substrate loading: 0.12 mmol for Methods A and C; 0.88 mmol for Method B. Yields determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

After this targeted optimization, we sought to evaluate the generality of this new protocol against the two previously developed systems for C–O activation in Suzuki-type cross-coupling. We assembled a set of twelve alkenyl carboxylates with varying leaving groups (acetate and pivalate) and coumarin, pyrone, lactone, and lactam scaffolds as part of an exhaustive experimental design (Figure 4). Method A was previously used for the Pd(II)-catalyzed C–O activation cross-coupling, Method B is the optimized Pd(OAc)₂/SPhos system, and Method C was used for Pd(0)-catalyzed C–O activation cross-coupling. For the formation of **2**, we observe the highest yield using Method B with the OPiv substrate, consistent with our multivariate optimization; however, Method B proved to be specific for this one system, failing to generate substantial product even for the structurally-related cyclopentanone **3**. To form **3**, only Method A with the OPiv substrate is effective, giving 62% solution yield.

Across these 36 reactions, several trends are apparent. Pivalate substrates are universally superior to the acetate substrates, which points to substrate decomposition as a potential issue in this chemistry. Method C, involving Pd(PCy₃)₂ as a single-component precatalyst, is the most general, giving >30% yield for every substrate other than the synthesis of **3**. More broadly, these results reveal the importance of evaluating multiple methods for a given target substrate set: each of the three methods here performs best for different cases (Method A for **3**, Method B for **2**, and Method C for **4-7**). Attempts to purify these compounds by chromatography or selective extractions led to either failure to remove pinacol-containing impurities, or decomposition of the product; therefore, characterization was performed on crude reaction products.

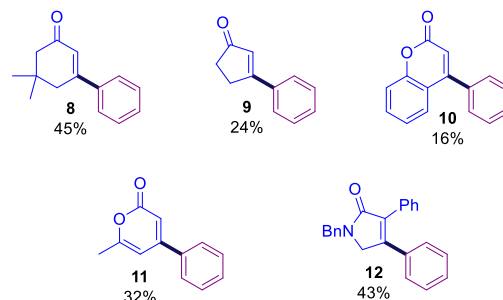
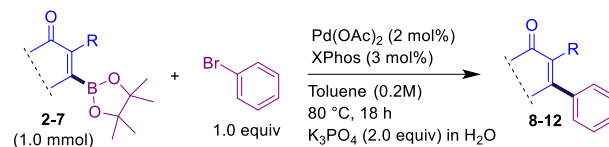
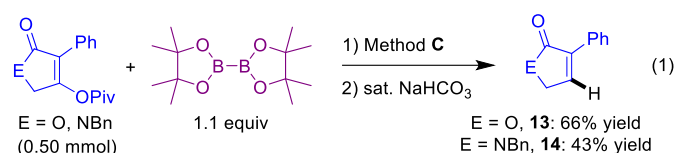
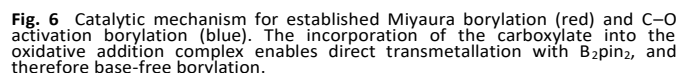


Fig. 5 Suzuki cross-coupling of prepared alkenyl boronates. Yields are for isolated compounds over two steps after column chromatography. Using boronate **6** gives poor reactivity due to near complete protodeboration under the reaction conditions.

To assess these alkenyl boronates in cross-coupling, we performed preparative-scale Suzuki reactions. First, a 1 mmol scale synthesis was conducted to form **2-7** using the optimal Method from Figure 4. We then performed a neutral aqueous workup of the crude boronate product, followed by a general and unoptimized Suzuki cross-coupling protocol (Figure 5). This enabled the isolation of the arylated products **8-11**. Unfortunately, boronates **6** and **7** resulted in either very low yield (using **6**: <2% isolated) or an inseparable mixture of cross coupling and protodeboration products (using **7**, 49% yield of a 3.33:1 mixture of **12** and **14**).²⁸ We discovered that **6** and **7** are very sensitive to aqueous base, undergoing complete protodeboration after treatment even with saturated NaHCO₃. Using this procedure, we isolated these products in 66% and 43% yield, respectively, which represents a two-step net deoxygenation of the parent enols (eq. 1).



With respect to mechanism, we propose that reactions involving Method C undergo sequential oxidative addition of the C–O bond, followed by direct transmetalation between the resulting Pd(II) carboxylate and B₂pin₂ (Figure 6). This contrasts with standard Miyaura borylation in that base is not required for the salt metathesis reaction to replace the (pseudo)halide after initial oxidative addition. Notably, we observe no homocoupling byproducts during borylation resulting from a tandem borylation/Suzuki sequence, wherein the product R–Bpin would undergo direct transmetalation with the palladium(II) carboxylate intermediate. This is in contrast to previous observations from our laboratory where rapid transmetalation/reductive elimination is observed with PhB(OH)₂.²³



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