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

Gregory Gaube, Nahiane Pipaon Fernandez, and David C. Leitch*

Department of Chemistry, University of Victoria, 3800 Finnerty Rd. Victoria BC, CANADA, V8P 5C2.

*dcleitch@uvic.ca

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 B_2pin_2 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).

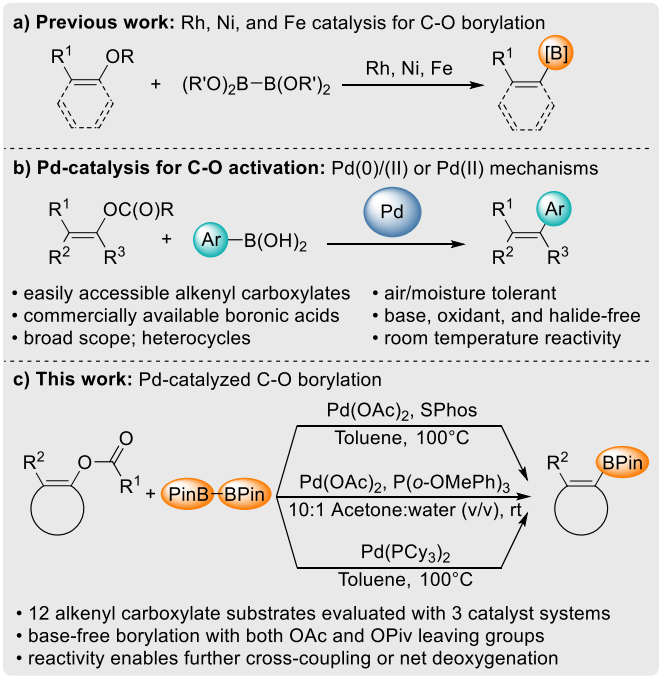
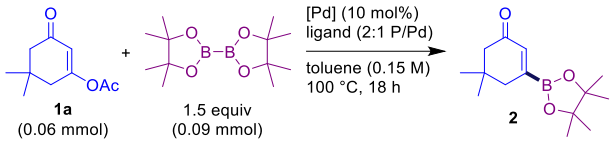


Fig. 1 a) Prior catalytic approaches to C–O borylation; b) C–O activation in C–C bond formation with arylboronic acids; c) an evaluation of catalytic systems for borylation involving C–O activation

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 $Pd(PCy_3)_2$, 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 B_2pin_2 and dimedone-derived alkenyl acetate **1a** (Figure 2).



Ligand	$Pd(OAc)_2$	$Pd_2dba_3 \cdot CHCl_3$	[Pd(acetanilide)OAc]$_2$	^{DMP}DAB-Pd-MAH	
$P(o\text{-}OMePh)_3$	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**

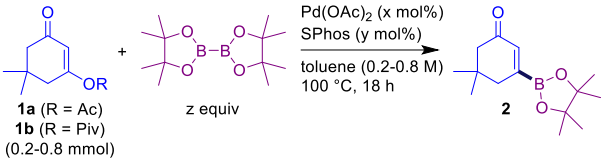
	$Pd(PCy_3)_2$	$(dppf)PdCl_2 \cdot DCM$	No Pd	No Pd or B_2Pin_2	
No Ligand	98	11	5	5	% Conv. **1a**
	62	4	0	0	% Yield **2**

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

Initially we evaluated the efficacy of four ligands, including the previously identified P(*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 ^{DMP}DAB–Pd–MAH,[27] and two Pd^{II} compounds. In addition, we evaluated two single-component precatalysts: $Pd(PCy_3)_2$ and $(dppf)PdCl_2$. 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 $Pd(OAc)_2$ and SPhos as the most active *in situ* candidate (78% conversion and 62% solution yield) for further optimization. $Pd(PCy_3)_2$ is also effective, with a similar solution yield (62%) though poorer mass balance.

Using the $Pd(OAc)_2$/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% $Pd(OAc)_2$, consistent with a monophosphine-Pd active catalyst.

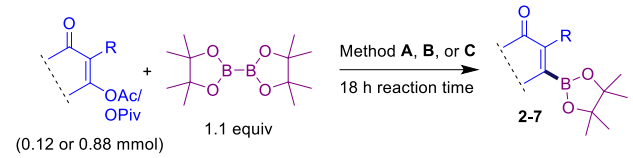
In all cases, **1a** conversion and yield of **2** is improved with a large excess of B_2Pin_2. Using this excess generally increases the yield more than the conversion, leading to better overall mass balance. With 0.2M of **1a**, 10 mol% $Pd(OAc)_2$, 15 mol% SPhos and 2.0 equivalents of B_2Pin_2 an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



Substrate	[1] (M)	$Pd(OAc)_2$ 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	
				2.0	40	25	
			3.0	1.1	30	1	
				2.0	40	19	
		7.5	1.5	1.5	58	33	Centerpoint
		10.0	1.5	1.1	66	40	
				2.0	89	71	Maximum
			3.0	1.1	74	44	
				2.0	92	62	
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 ^{1}H 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 [**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 the chemical yield of **2** being reduced to only 44% at [**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**: $Pd(PCy_3)_2$ (10 mol%), toluene (0.2 M), 100 °C

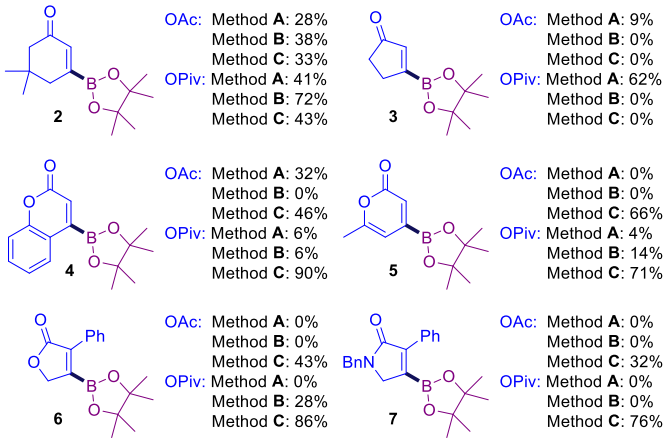


Fig. 4 Comparison of Pd-catalyzed methods for the borylation of alkenyl acetate and pivalate substrates. Substrate loading: 0.12 mmol for Methods A and C; 0.88 mmol for Method B. Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

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 $Pd(PCy_3)_2$ 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, so characterization was performed on crude reaction products.

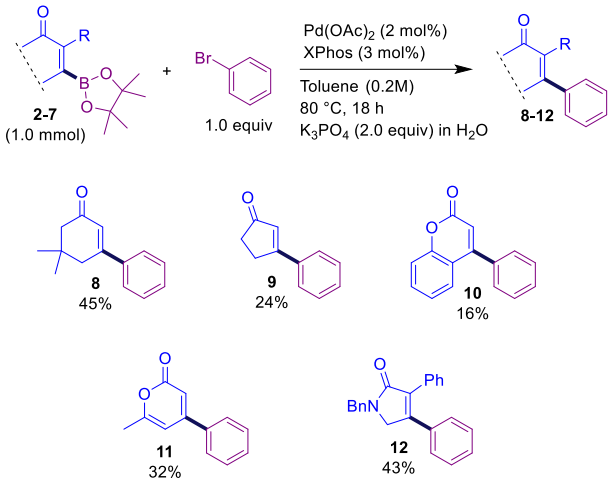


Fig. 5 Suzuki cross-coupling of prepared alkenyl boronates. Yields are for isolated compounds over two steps after column chromatography. Using boronate **6** gives poor reactivity due to near complete protodeboronation under the reaction conditions.

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. During these investigations we discovered that even a mildly basic aqueous workup of these alkenyl boronates (saturated $NaHCO_3$) prior to cross-coupling results in substantial protodeborylation. While this does provide a potentially simple two-step method for net deoxygenation of the β-dicarbonyl precursors (via acylation then Pd-catalyzed borylation/protodeborylation), it is problematic for realizing cross-coupling catalysis. We largely circumvented this issue by performing a neutral aqueous workup of **2**-**7**, followed by a general and unoptimized Suzuki cross-coupling protocol (Figure 5). This enabled the isolation of the arylated products **8**-**12**, despite the observed instability of the boronates; boronate **6** did prove to be too unstable toward protodeborylation for cross-coupling to be successful.

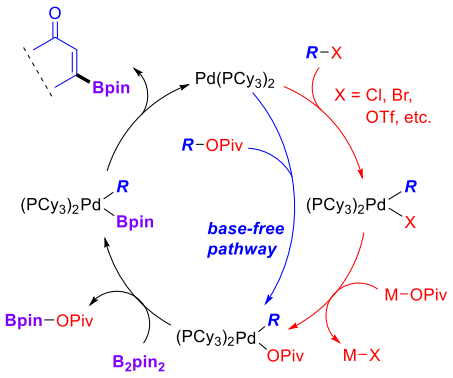


Fig. 6 Catalytic mechanism for established Miyaura borylation (red) and C–O activation borylation (blue). The incorporation of the carboxylate into the oxidative addition complex enables direct transmetallation with B_2pin_2, and therefore base-free borylation.

With respect to mechanism, we propose that reactions involving Method C undergo sequential oxidative addition of the C–O bond, followed by direct transmetallation between the resulting Pd(II) carboxylate and B_2pin_2 (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 transmetallation with the palladium(II) carboxylate intermediate. This is in contrast to previous observations from our laboratory where rapid transmetallation/reductive elimination is observed with $PhB(OH)_2$.[23]

Conclusions

Through a targeted multivariate optimization and an extensive parallel evaluation of conditions and substrates, we have demonstrated the base-free, Pd-catalyzed borylation of alkenyl carboxylates. Depending on the nature of the substrate, different catalyst/solvent combinations are most effective, with alkenyl pivalates outperforming their acetate counterparts. The resulting alkenyl boronates have varying stability with respect to protodeboronation, but still undergo Suzuki cross-coupling. This base-free borylation is enabled by the direct oxidative addition of the substrate to Pd(0), giving a Pd(II) carboxylate that can undergo direct transmetallation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge with respect the Lekwungen peoples on whose traditional territory the University of Victoria (UVic) stands, and the Songhees, Esquimalt and WSÁNEĆ peoples whose historical relationships with the land continue to this day. The authors thank UVic, NSERC, CFI, BCKDF, and MITACS (RTA to GG) for funding this work.

Notes and references

1 J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177–2250.
2 E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott and T. B. Marder, *Chem. Rev.*, 2016, **116**, 9091–9161.
3 D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458.
4 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508–7510.
5 T. Ishiyama and N. Miyaura, *J. Organomet. Chem.*, 2000, **611**, 392–402.
6 M. Wang and Z. Shi, *Chem. Rev.*, 2020, **120**, 7348–7398.
7 S. Barroso, M. Joksch, P. Puylaert, S. Tin, S. J. Bell, L. Donnellan, S. Duguid, C. Muir, P. Zhao, V. Farina, D. N. Tran and J. G. de Vries, *J. Org. Chem.*, 2021, **86**, 103–109.
8 D.-G. Yu, B.-J. Li and Z.-J. Shi, *Acc. Chem. Res.*, 2010, **43**, 1486–1495.
9 B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346–1416.
10 B.-J. Li, D.-G. Yu, C.-L. Sun and Z.-J. Shi, *Chem. Eur. J.*, 2011, **17**, 1728–1759.
11 M. Tobisu and N. Chatani, *Top. Curr. Chem.*, 2016, **374**, 41.
12 Z. Qiu and C.-J. Li, *Chem. Rev.*, 2020, **120**, 10454–10515.
13 H. Kinuta, J. Hasegawa, M. Tobisu and N. Chatani, *Chem. Lett.*, 2014, **44**, 366–368.
14 H. Kinuta, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2015, **137**, 1593–1600.
15 K. Huang, D.-G. Yu, S.-F. Zheng, Z.-H. Wu and Z.-J. Shi, *Chem. Eur. J.*, 2011, **17**, 786–791.
16 C. Zarate, R. Manzano and R. Martin, *J. Am. Chem. Soc.*, 2015, **137**, 6754–6757.
17 K. Nakamura, M. Tobisu and N. Chatani, *Org. Lett.*, 2015, **17**, 6142–6145.
18 M. Tobisu, J. Zhao, H. Kinuta, T. Furukawa, T. Igarashi and N. Chatani, *Adv. Synth. Catal.*, 2016, **358**, 2417–2421.
19 X. Zeng, Y. Zhang, Z. Liu, S. Geng, Y. He and Z. Feng, *Org. Lett.*, 2020, **22**, 2950–2955.
20 S. Geng, J. Zhang, S. Chen, Z. Liu, X. Zeng, Y. He and Z. Feng, *Org. Lett.*, 2020, **22**, 5582–5588.
21 J. Becica and D. C. Leitch, *Synlett*, 2021, **32**, 641–646.
22 G. Toupalas and B. Morandi, *ChemRxiv*, 2021, DOI:10.26434/chemrxiv.14217314.v1.
23 J. Becica, G. Gaube, W. A. Sabbers and D. C. Leitch, *Dalton Trans.*, 2020, **49**, 16067–16071.
24 J. Becica, O. R. J. Heath, C. H. M. Zheng and D. C. Leitch, *Angew. Chem. Int. Ed.*, 2020, **59**, 17277–17281.
25 S. E. Shockley, J. C. Holder and B. M. Stoltz, *Org. Process Res. Dev.*, 2015, **19**, 974–981.
26 A.-L. Lee, *Org. Biomol. Chem.*, 2016, **14**, 5357–5366.
27 J. Huang, M. Isaac, R. Watt, J. Becica, E. Dennis, M. I. Saidaminov, W. A. Sabbers and D. C. Leitch, *ACS Catal.*, 2021, **11**, 5636–5646.