J. Becica, D. C. Leitch

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C–O Bond Activation as a Strategy in Palladium-Catalyzed Cross-Coupling

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Abstract The activation of strong C–O bonds in cross-coupling catalysis can open up new oxygenate-based feedstocks and building blocks for complex-molecule synthesis. Although Ni catalysis has been the major focus for cross-coupling of carboxylate-based electrophiles, we recently demonstrated that palladium catalyzes not only difficult C–O oxidative additions but also Suzuki-type cross-couplings of alkenyl carboxylates under mild conditions. We propose that, depending on the reaction conditions, either a typical Pd(0)/(II) mechanism or a redoxneutral Pd(II)-only mechanism can operate. In the latter pathway, C–C bond formation occurs through carbopalladation of the alkene, and C– O cleavage by β -carboxyl elimination.

- 1 Introduction
- 2 A Mechanistic Challenge: Activating Strong C–O Bonds
- 3 Exploiting Vinylogy for C–Cl and C–O Oxidative Additions
- 4 An Alternative Mechanism for Efficient Cross-Coupling Catalysis
- 5 Conclusions and Outlook

Key words cross-coupling, C–O activation, palladium catalysis, vinylogy, oxidative addition, carbopalladation

1 Introduction

Engaging a wider array of electrophiles in metal-catalyzed cross-coupling reactions continues to be an important goal in synthetic methods development.¹ Whereas the nature of the nucleophile (be it organometallic or otherwise) often defines the reaction class,^{2–5} the nature of the electrophile is equally important in determining reactivity and mechanism. Typical electrophiles used in cross-coupling reactions are the ubiquitous organo(pseudo)halides (–I, –Br, –Cl, –OSO₂R), which undergo (relatively) well-understood oxidative addition⁶ reactions with transition-metal catalysts, such as those based on Pd^{7–14} or Ni.^{15–21} Expanding the scope of suitable electrophiles beyond (pseudo)halides to those with oxygen-based leaving groups offers opportunities to improve reaction mass efficiency, remove



Joseph Becica (*left*) is a native of New Jersey, USA. He obtained his Ph.D. in organometallic chemistry in 2019 from Temple University (Philadelphia, USA) in the group of Professor Graham Dobereiner, developing methods for organic reactions catalyzed by palladium and molybdenum. During this time, he was also a visiting researcher at GlaxoSmithKline, where he first worked with Dave Leitch on a collaborative project on challenging C–N couplings. Previously, he studied organometallic chemistry in the groups of Nathan West at the University of the Sciences (Philadelphia, USA) and Professor Ola Wendt at Lund University (Lund, Sweden). He joined the Leitch group at the University of Victoria in 2019 as a New Frontiers Postdoctoral Fellow.

David C. Leitch (right) grew up on Vancouver Island, BC, and obtained both his B.Sc. (2004) and Ph.D. (2010) at the University of British Columbia, Vancouver (Canada). There, he worked with Professor Laurel Schafer on organozirconium chemistry and hydroamination catalysis. He then held a postdoctoral position at McGill University (2010-2012), working with Professor Bruce Arndtsen on a multicomponent approach to building conjugated organic materials. In 2012, Dave obtained an NSERC Postdoctoral Fellowship to work with Professor John Bercaw and Dr. Jay Labinger at the California Institute of Technology (USA) (2012-2014) on tandem catalysis for alkane functionalization. In 2014, he joined GlaxoSmithKline's Catalysis Center of Excellence at Research Triangle Park, NC (USA), and then moved with the group to Pennsylvania in 2015. There he became group leader of the rechristened Chemical Catalysis group (2016–2018), as well as the Continuous Primary group (2017–2018). In 2019, Dave returned home as an assistant professor at the University of Victoria (Canada). His research group is focused on mapping chemical reaction space by using high-throughput experimentation, and developing new catalysts and catalytic reactions for complex-molecule synthesis.

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J. Becica, D. C. Leitch

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hazardous upstream halogenation processes, and open up new feedstocks (Scheme 1a);²²⁻²⁷ however, there are significant unmet challenges and knowledge gaps with respect to reaction and catalyst design. In this account, we describe our initial efforts in pursuing a C–O bond-activation strategy for developing new Pd-catalyzed transformations, specifically by enabling Suzuki-type cross-couplings of alkenyl carboxylates, an attractive yet challenging class of electrophiles, under surprisingly mild conditions.^{28,29}

2 A Mechanistic Challenge: Activating Strong C–O Bonds

In moving from breaking C–X bonds to C–O bonds during cross-coupling catalysis, there are several linked challenges. From a kinetic standpoint, the C–O bonds in question are generally quite strong (~100–110 kcal/mol), making oxidative addition to a low-valent organometallic species difficult.²² There is a prevailing view in the field that Pd catalysts are less able (or unable) to achieve the required C–O oxidative additions;²⁶ as a result, the community has focused on Ni catalysis, as low-valent Ni generally undergoes oxidative addition reactions more readily than does Pd.^{6,15,16,24,30} Seminal work on Ni-catalyzed cross-coupling with O-based electrophiles by Snieckus and co-workers (using Grignard reagents)³¹ and later by the Garg³² and Shi^{33,34} groups (using boronic acids or zinc reagents) led to an explosion of research on Ni-based systems.^{1,15,16,22-25,35}



electrophiles: opportunities and challenges

A second significant challenge specific to the use of carboxylate-based electrophiles is achieving chemoselectivity. Whereas the C–O bond that requires activation is strong, C(acyl)–O bonds are significantly weaker (~80 kcal/mol), and there are many kinetically accessible pathways for acyl substitution (Scheme 1). These include metal-catalyzed reactions (e.g., the acyl-Suzuki reaction^{36–41} or decarbonylative cross-couplings^{42–45}) and substrate decomposition by simple hydrolysis or transesterification. From the perspective of oxidative addition, there is some hope: breaking the stronger C–O bond should be thermodynamically favored, as a stronger M–O bond results. Notably, there is evidence to support this assertion for Ni systems.^{30,42,46–48} Even with thermodynamics on our side, the kinetic accessibility of C(acyl)–O activation could potentially divert the course of catalysis.

Finally, we would like to address the question 'why Pd?', especially in light of the general view that the field should be moving away from precious metals toward Earth-abundant metals.⁴⁹ and the specific view that Ni should be superior to Pd for C–O bond activation. The synthesis of complex molecules as low-volume high-value products (such as pharmaceuticals, agrochemicals, or advanced materials) requires robust, efficient, and economical chemical processes that work for highly functionalized substrates. Despite the high cost and low natural abundance of Pd. organopalladium catalysis offers many distinct advantages, including excellent functional-group tolerance,^{50,51} relatively high catalytic efficiency (i.e., low catalyst loadings), and the ability to act in the presence of water or even air. To us, discovering and exploiting complementary reactivity with both precious- and abundant-metal catalysts is an important goal. Process economics and sustainability are case-dependent, and we in the academic community should do our best to provide our industry-based colleagues with as many options as possible.

3 Exploiting Vinylogy for C–Cl and C–O Oxidative Additions

The inspiration for our initial foray into Pd-catalyzed cross-coupling through C-O activation came from an industrial project carried out at GlaxoSmithKline. The seemingly simple problem of how to prepare α,β -unsaturated- γ -keto esters in a redox-neutral manner alerted us to the potential of exploiting vinvlogy⁵² in reaction and substrate design. To access the target keto esters, we developed a Pd-catalyzed carbonylative esterification of β -chloroenone derivatives, i.e. vinylogous acyl chlorides.⁵³ Although carbonylation of typical aryl and vinyl chlorides is challenging^{54,55} due to turnover-limiting oxidative addition,56 through highthroughput experimentation we discovered many effective catalyst systems for carbonylating β -chloroenones.^{57,58} These reactions proceed with low Pd loadings (down to 0.5 mol%), use simple trialkylphosphines $[PCy_3, P(t-Bu)_3, or$ $PMe(t-Bu)_2$], and work on ≥ 1 g scales to produce many synthetically versatile γ -keto esters (Scheme 2). Subsequent mechanistic studies revealed rapid oxidative addition of the β -chloroenones to Pd(0), which we attribute to both precoordination of the C=C bond and the increased electrophilicity at C_{β} due to the vinylogous ketone.

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J. Becica, D. C. Leitch

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Scheme 2 Pd-catalyzed carbonylation of β -chloroenones enabled by rapid oxidative addition of vinylogous substrates to Pd(0)

Given all the aforementioned challenges associated with C–O oxidative addition for aryl and alkenyl carboxylate cross-couplings, we reasoned that exploiting vinylogy in substrate design might provide new C–O activation and functionalization chemistry with Pd (Scheme 3). By analogy to the earlier carbonylation chemistry, we targeted vinylogous anhydrides, formed by O-acylation of β -keto esters and diketones, as a reactive class of alkenyl carboxylates. In contrast to alkenyl halides, which are generated by using toxic and/or high-energy reagents [SOCl₂, (COCl)₂, PX₃ or POX₃, PPh₃/Br₂], alkenyl carboxylates are readily prepared under relatively mild conditions by using acyl chlorides and/or anhydrides (basic conditions) or isopropenyl acetate (acid-catalyzed).



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To assess the possibility of C–O oxidative addition with these vinylogous substrates, we tested several carboxylates derived from a pyrone (1), a coumarin (2), or a cyclohex-2-en-1-one (3) scaffold in combination with $Pd(PCy_3)_2$ as a reactive Pd(0) source (Scheme 4).²⁸ From this initial work, we determined not only that C–O oxidative addition is fea-

sible with this Pd(0) complex, but also that both C(acvl)-O(undesired) and C(alkenyl)-O (desired) bonds undergo addition to Pd. With the pyrone acetate 1a and the coumarin acetate 2, C(acyl)-O cleavage occurs rapidly at room temperature to give the corresponding Pd(II) acyl complexes; however, upon heating, these complexes are transformed into the Pd(II) alkenyl species. In other words, oxidative addition of the weaker C-O bond is kinetically favored, whereas oxidative addition of the stronger, desired C-O bond is thermodynamically favored. This is entirely consistent with previous observations with Ni, 30,42,46-48 but is the first time such behavior has been observed with Pd. This promising reactivity is nevertheless complicated by the kinetic accessibility of C(acyl)–O cleavage. In contrast, oxidative addition experiments with the pyrone pivalate **1b** and the cyclohexenyl acetate **3** revealed no C(acyl)–O cleavage at room temperature, and only C(alkenyl)–O oxidative addition at elevated temperature. Thus, both the steric nature and the electronic nature of the carboxylate group influence the accessibility of these two oxidative addition pathways.



Scheme 4 Oxidative addition of C–O bonds to Pd(0): kinetic versus thermodynamic selectivity is dependent on temperature and structure.

Encouraged by these results, we sought a proof-of-concept for cross-coupling with these substrates by using Pd(0)catalysis.²⁹ Because of their many potential advantages. alkenyl carboxylates have been previously explored as cross-coupling partners by several groups, including those of Shi,^{34,59} Ackermann,⁶⁰ von Wangelin,⁶¹ and Knochel.^{62,63} These reactions generally rely on Earth-abundant metal catalysts, including systems based on Ni, Co, Cr, or Fe, along with hard organometallic nucleophiles, such as Mg or Zn reagents. With our stated goal of developing complementary catalytic methods in mind, we recognized the need for systems capable of coupling less sensitive nucleophiles. Organoboronic acids are extremely versatile in cross-coupling, with myriad building blocks commercially available. Although there are a few examples of successful couplings between alkenyl carboxylates and boronic acids (using Ni,⁶⁴ Rh,^{65,66} or Pd⁶⁷), these systems tend to have a relatively limited scope. For example, the single previous example using exclusive Pd catalysis operates with vinyl acetate itself.⁶⁷

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By using $Pd(PCy_3)_2$ as a Pd(0) precatalyst, we were indeed able to cross-couple several alkenyl acetates and pivalates with simple arylboronic acids (Scheme 5).²⁹ Although these reactions required elevated temperatures and high Pd loadings (10 mol%), we noted that they proceeded in the absence of exogenous base.⁶⁸ Standard Suzuki coupling with halide-based electrophiles generally operate through a salt metathesis-transmetalation sequence, where the Pd(II) halide intermediate is converted into a Pd(II) hydroxide before transmetalation occurs.⁶⁹ In the present system, C-O oxidative addition at Pd(0) instead produces a Pd(II) carboxylate intermediate that directly undergoes transmetalation. In other words, no intervening salt metathesis or boronic acid activation⁷⁰ is required, which permits base-free cross-coupling. Carboxylate electrophiles are therefore advantageous from both a feedstock perspective (as in Scheme 1) and a reactivity perspective. Our initial conditions, especially the need for large amounts of a sensitive and expensive Pd(0)precatalyst, do, however, leave much to be desired from the standpoint of practicality.

4 An Alternative Mechanism for Efficient Cross-Coupling Catalysis

During the course of our investigation into oxidative addition reactivity using Pd(0), we pursued a parallel effort to identify potential catalyst systems for the aforementioned user-friendly catalyst system capable of operating at or near room temperature without the need for an inert atmosphere. Through an iterative screening and optimization process (Scheme 6 is representative), we identified the combination of Pd(OAc)₂ and (*o*-MeOC₆H₄)₃P as an effective catalyst system for a model cross-coupling reaction.²⁹



Scheme 5 Proof-of-concept for base-free Suzuki coupling via oxidative addition of C–O bonds to Pd(0), with mechanistic proposal

During further development of the reaction conditions, we observed variable reactivity depending on the particular arylboronic acid used and even on the particular batch of a specific arylboronic acid. We attribute this to varying quantities of the corresponding boroxine (i.e. boronic acid anhydride) in the commercial materials. By refining the reaction conditions, we identified a protocol that leads to reproducible reactivity for a broad scope of substrates. Acetone-H₂O (10:1) is generally an effective solvent system that fully dissolves and hydrates the boronic acid. A Pd/(o-MeOC₆H₄)₂P ratio of 1:1.5 is optimal at catalyst loadings as low as 0.5 mol% Pd, although our typical conditions for scope exploration employed 4 mol% Pd. The reactions are generally performed at room temperature under air and in the absence of an exogenous base. Using these conditions, we synthesized various substituted cyclic enones through cross-coupling in good to excellent isolated yields (40-99%; Scheme 7). These conditions permit the presence of various functional groups, including potentially base-sensitive ones. Aryl chlorides and bromides appear to be compatible with this chemistry, which is noteworthy for a Pd-catalyzed reaction.

Given the observed chemoselectivity for substitution at the alkenyl acetate rather than an aryl halide, and the mild operating conditions relative to those observed with a Pd(0) precatalyst (Scheme 5), we considered a Pd(0)/(II)-based mechanism unlikely. Instead, we proposed a redox-neutral Pd(II) pathway for the Pd(OAc)₂/(o-MeOC₆H₄)₃P catalyst combination (Scheme 8). Here, transmetalation of ArB(OH)₂ to an L_nPd^{II}(OAc) species generates a Pd(II)-aryl complex Downloaded by: Karolinska Institutet. Copyrighted material.

J. Becica, D. C. Leitch



that can undergo carbopalladation across the C=C double bond of the alkenyl acetate. For the cyclic substrates that we

investigated, epimerization of the resulting Pd(enolate) via the O-bound isomer brings the Pd atom and the acetoxy group into a *syn*-confirmation, permitting β -acetoxy elimination to release the cross-coupled product and regenerate $L_nPd^{II}(OAc)$. We note that similar mechanisms have been proposed for the aforementioned Rh^{65,66} and Pd-catalyzed⁶⁷ couplings of alkenyl acetates and boronic acids, as well as for related chemistries including Pd-catalyzed conjugate addition⁷¹⁻⁷⁴ and oxidative Heck coupling.^{75,76}



Scheme 8 Proposed mechanism for cross-coupling of alkenyl acetates with arylboronic acids by using Pd(II) precatalysts

As part of a preliminary study of the feasibility of this alternative mechanism, we evaluated a series of Pd precursors in the model reaction shown in Scheme 6 at both 23 °C and 60 °C. As a model for the key Pd–aryl intermediate generated by the initial transmetalation, we employed the known complex $[(o-MeOC_6H_4)_3P]Pd(OAc)(Ph)^{77}$ as a precatalyst. Use of this complex resulted in excellent reactivity in the catalytic reaction, giving >99% yield at 23 °C in one hour. Only the combination of Pd(OAc)₂ and $(o-MeOC_6H_4)_3P$

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gave a comparable reactivity. Notably, when $Pd_2(dba)_3$ ·CH-Cl₃ was used as the Pd source, no product was observed at 23 °C; however, an 87% yield of the product was obtained at 60 °C, likely through a variation of the catalytic cycle shown in Scheme 5. As both Pd(0)/(II) and Pd(II)-only mechanisms appear to operate, depending on the Pd source used, we are currently exploring both avenues to enable new reaction and catalyst development toward complex-molecule synthesis.

5 Conclusions and Outlook

Through a combination of fundamental organometallic chemistry and catalytic reaction design, we have developed methods to engage alkenyl carboxylates in Pd-catalyzed cross-couplings. C-O oxidative addition with alkenyl carboxvlates is feasible at Pd(0), with selectivity for C(acvl)-Oversus C(alkenyl)–O activation, depending on the reaction conditions and substrate structure. In addition, the catalytic reactivity that we observe indicates that an alternative mechanism to the standard Pd(0)/(II) cycle can operate when using a Pd(II) precursor. Importantly, catalysis in this regime is robust, mild, base-free, and tolerant of air, water, and a variety of potentially sensitive functional groups. This methodology is therefore complementary to other important cross-coupling reactions that employ first-row transition metals as catalysts. In-depth synthetic and mechanistic studies are underway to achieve a more thorough understanding of these catalytic systems, particularly the dichotomy between the proposed Pd(0)-mediated and Pd(II)-mediated pathways. By taking advantage of these two general reaction pathways, we aim to expand the scope of amenable coupling partners and to deploy this method toward complex-molecule synthesis.

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J. Becica, D. C. Leitch

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