

Interrogating Pd(II) anion metathesis using a bifunctional chemical probe: A transmetalation switch

John J. Molloy,^a Ciaran P. Seath,^a Matthew J. West,^a Calum McLaughlin,^a Neal J. Fazakerley,^b Alan R. Kennedy,^a David J. Nelson,^a and Allan J. B. Watson^{a*}

^aDepartment of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK.

^bGlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK.

Supporting Information Placeholder

ABSTRACT: Ligand metathesis of Pd(II) complexes is mechanistically essential for cross-coupling. We present a study of halide→OH anion metathesis of (Ar)Pd(II) complexes using vinylBPin as a bifunctional chemical probe with Pd(II)-dependent cross-coupling pathways. We identify the variables that profoundly impact this event and allow control to be leveraged. This then allows control of cross-coupling pathways *via* promotion or inhibition of organoboron transmetalation, leading to either Suzuki-Miyaura or Mizoroki-Heck products. We show how this transmetalation switch can be used to synthetic gain in a cascade cross-coupling/Diels-Alder reaction, delivering borylated or non-borylated carbocycles, including steroid-like scaffolds.

Ligand metathesis at catalytically generated (Ar)Pd(II) complexes is an essential mechanistic event that underpins the most widely employed catalytic processes, such as the Suzuki-Miyaura, Negishi, and Mizoroki-Heck reactions.¹ A pertinent example is the X→OH anion metathesis of (Ar)Pd(II)(X) complexes (where X = halide), which enables oxopalladium transmetalation in the Suzuki-Miyaura reaction.²⁻⁹ In seminal studies by Hartwig, stoichiometrically prepared (Ar)Pd(II)(OH) complexes were shown to engage organoboron compounds and thereby provide key evidence to support oxopalladium transmetalation (Scheme 1a).⁵ Contemporaneously, Amatore and Jutand provided compelling evidence for the same complexes and pathway in solution using electrochemical methods.⁶ More recently, Denmark unequivocally demonstrated the role of (Ar)Pd(II)(OH) complexes in oxopalladium transmetalation using rapid injection low temperature NMR techniques to detect the elusive pretransmetalation intermediates.⁸

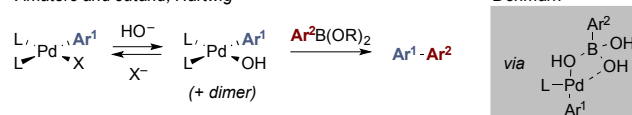
The essential role of (Ar)Pd(II)(OH) complexes for organoboron transmetalation renders X→OH anion metathesis a critical mechanistic event, and highlights the different reactivity modes of (Ar)Pd(II) based on the associated anion. Designed manipulation of this event may provide a powerful, yet untapped, control vector in Pd catalysis for the chemoselective manipulation of multi-reactive systems and control of transmetalation more generally.

Here we describe the use of a bifunctional chemical probe to interrogate X→OH anion metathesis of (Ar)Pd(II)(X) complexes (Scheme 1b). We show how this event can be controlled to allow selection of Suzuki-Miyaura or Mizoroki-Heck cross-coupling pathways on a bifunctional template leading to development of a chemoselective triene cascade annulation that provides borylated or non-borylated carbocycles (Scheme 1c).

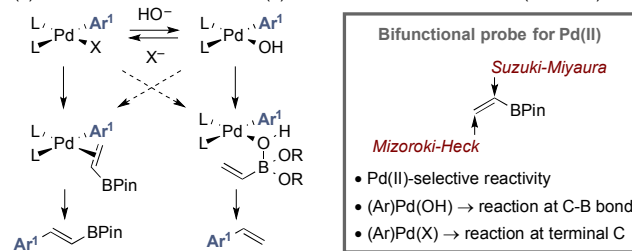
The groundbreaking studies by Hartwig,⁵ Amatore and Jutand,⁶ and Denmark⁸ used stoichiometrically prepared Pd(II) complexes

and/or spectroscopic methods to interrogate oxopalladium transmetalation, with each of these studies providing key insight into this previously ambiguous process. The Hartwig study provided the most detail on anion metathesis; specifically, equilibrium constants for OH→X exchange of (R₃P)₂Pd(Ar)(OH) using *n*-Bu₄NX in H₂O/THF (R = Cy, Ph; X = I, Br, Cl).^{5,10}

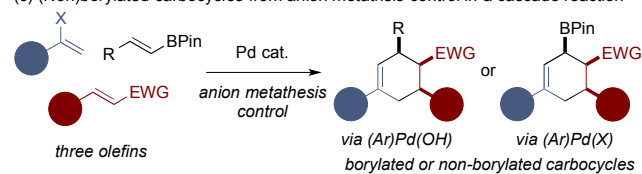
(a) Anion metathesis and oxopalladium transmetalation of organoborons Amatore and Jutand, Hartwig Denmark



(b) A transmetalation switch at Pd(II) via control of anion metathesis (this work)



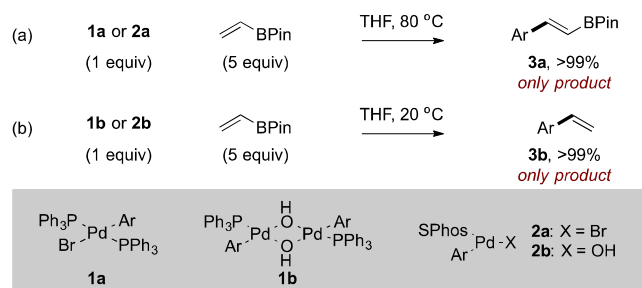
(c) (Non)borylated carbocycles from anion metathesis control in a cascade reaction



Scheme 1. Anion metathesis of (Ar)Pd(II)(X). (a) Organoboron transmetalation; (b) Control of anion metathesis using a bifunctional probe; and (c) utility in a triene cascade annulation.

In this context, we hypothesized that additional reactivity-relevant information on this event may be obtained using a chemical probe approach. (Ar)Pd(II)(X) complexes are known intermediates for many Pd-catalyzed reactions, including the Mizoroki-Heck reaction.^{1,11} Accordingly, use of an appropriately selective chemical probe capable of Mizoroki-Heck *via* (Ar)Pd(II)(X) or Suzuki-Miyaura *via* (Ar)Pd(II)(OH) would give a pathway selectivity response based on the (Ar)Pd(II) species present in solution and the relative rates of reaction. To this end, vinylBPin is a competent organoboron nucleophile for Suzuki-Miyaura and is known to undergo Mizoroki-Heck at the terminal carbon.¹²

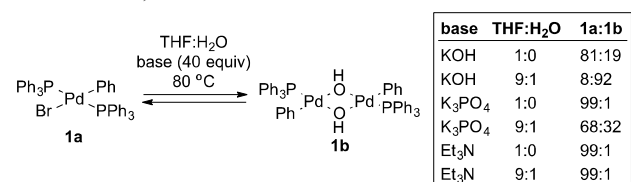
To demonstrate its suitability as a chemical probe, we exposed vinylBPin to stoichiometric (Ph₃P)₂(Ar)Pd(II)(Br) (**1a**), (SPhos)(Ar)Pd(II)(Br) (**2a**), [(Ph₃P)(Ar)Pd(II)(μ-OH)]₂ (**1b**), and (SPhos)(Ar)Pd(II)(OH) (**2b**) (Scheme 2).



Scheme 2. Stoichiometric reactions of Pd(II) complexes with vinylBPIn. Ar = 4-FC₆H₄. Determined by ¹⁹F NMR. **1b** includes *cis* and *trans*. **2a/2b** include monomer/dimer.

1a and **2a** provided **3a** as the only coupling product, while **1b** and **2b** delivered only **3b**. Use of a mono-deuterio labeled vinylBPIn ruled out *cine* substitution, supporting only Suzuki-Miyaura and Mizoroki-Heck as the operational pathways (see Supporting Information). While Suzuki-Miyaura was complete in 5 min at rt, the Heck process required heating and extended reaction times for meaningful conversion: *t*_{1/2} for vinylBPIn with **1a** was *ca.* 50 min at 353 K, while *ca.* 2 min at 293 K with **1b**, demonstrating a substantial difference in relative rate.¹³

To set a foundation for gaining control over cross-coupling pathways as a function of anion metathesis, we assessed the impact of base, temperature, and [H₂O] on the distribution of **1a** and **1b** in isolation, using reaction-like base: Pd stoichiometry (Scheme 3 and Chart 1).



Scheme 3. Effect of base and H₂O on (Ar)Pd(II) concentration. Determined by ³¹P NMR.

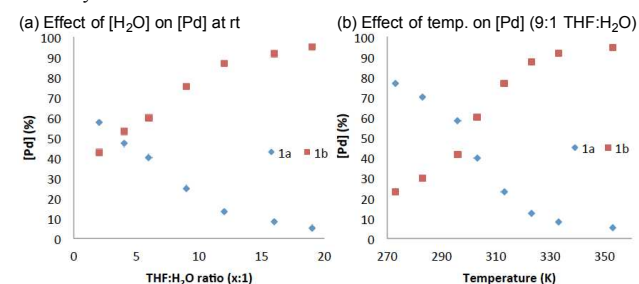


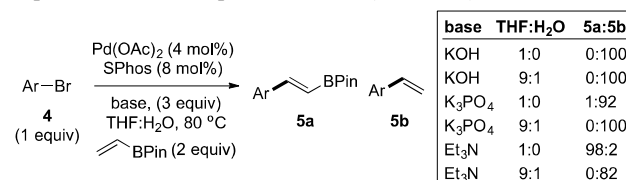
Chart 1. Impact of [H₂O] (a) and temperature (b) on the relative concentrations of **1a** and **1b** in the presence of KOH. Determined by ³¹P NMR.

Under dry conditions, **1a** predominated for all bases. However, when H₂O was added, the distribution of **1a** and **1b** varied as a function of the base (see SI for the full range of bases). KOH now favored **1b**, K₃PO₄ provided *ca.* 2:1 ratio of **1a**:**1b**, while Et₃N continued to favor **1a**. Using KOH, lower [H₂O] and elevated temperatures favored **1b** (Chart 1), with the former consistent with Hartwig's observations.⁵ Accordingly, the Pd(II) speciation is profoundly affected by both an aqueous basic medium and temperature.

There are two implications of this data: (1) For oxopalladium transmetalation, hydroxypalladium (*e.g.*, **1b**) and a neutral organoboron are required. From these data, lower [H₂O] favors increased [(Ar)Pd(II)(OH)]. In a landmark study of Suzuki-Miyaura cross-coupling of potassium organotrifluoroborates, Lloyd-Jones reported that lower [H₂O] favors higher concentrations of the boronic acid, with increasing [H₂O] favoring the boronate.¹⁴ Moreover, in basic biphasic systems, such as those

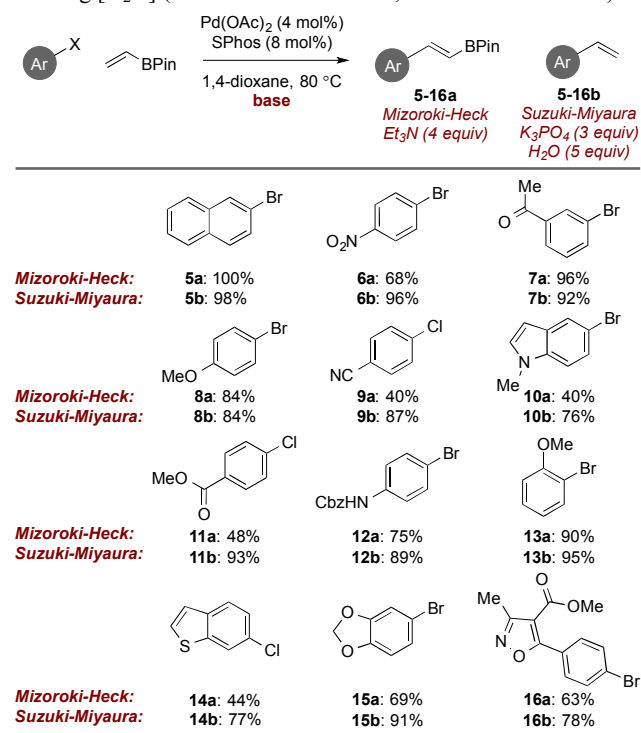
commonly employed for Suzuki-Miyaura, the boronate more readily distributes to the aqueous phase where protodeboronation can occur upon heating.^{15,16} Accordingly, for effective Suzuki-Miyaura, at least in the mechanistic sense, low [H₂O] would appear to be more favorable. (2) The Mizoroki-Heck of vinylBPIn requires thermal promotion. However, this then requires the system to be strictly anhydrous. Adventitious H₂O and elevated temperatures favor higher [**1b**] (Chart 1), and based on the stark difference in relative rate (Suzuki-Miyaura *t*_{1/2} = 2 mins (rt); Mizoroki-Heck *t*_{1/2} = 50 min (80 °C)), this will favor the Suzuki-Miyaura pathway. Again, from the mechanistic standpoint, anhydrous conditions with organic base favors (Ar)Pd(II)(X), which will promote the Mizoroki-Heck.

With a functional understanding of how the metathesis event can be manipulated, we used vinylBPIn to probe the outcome of control in a catalytic scenario using SPhos to allow subsequent exploration of electrophile influence (Scheme 4).



Scheme 4. Catalytic reactions with vinylBPIn with variation of H₂O and base. Ar = 2-naphthyl. Determined by ¹H NMR.

Regardless of the presence of H₂O, the stronger bases (KOH, K₃PO₄) favored the Suzuki-Miyaura pathway. Adventitious H₂O arising from the hygroscopic bases may be a contributing factor.^{17,18} Alongside the recorded difference in half-life in the stoichiometric experiments, this suggests a kinetic effect where low [Pd(OH)] outcompetes the Pd(X)-promoted Heck pathway. This was reinforced from the results using Et₃N. Under dry conditions, Heck is operational; however, despite **1a** predominating in the aqueous system (Scheme 3), Suzuki-Miyaura increases with increasing [H₂O] (9:1 shown in Scheme 4; see SI for full details).



Scheme 5. Generality of speciation control under catalytic conditions.

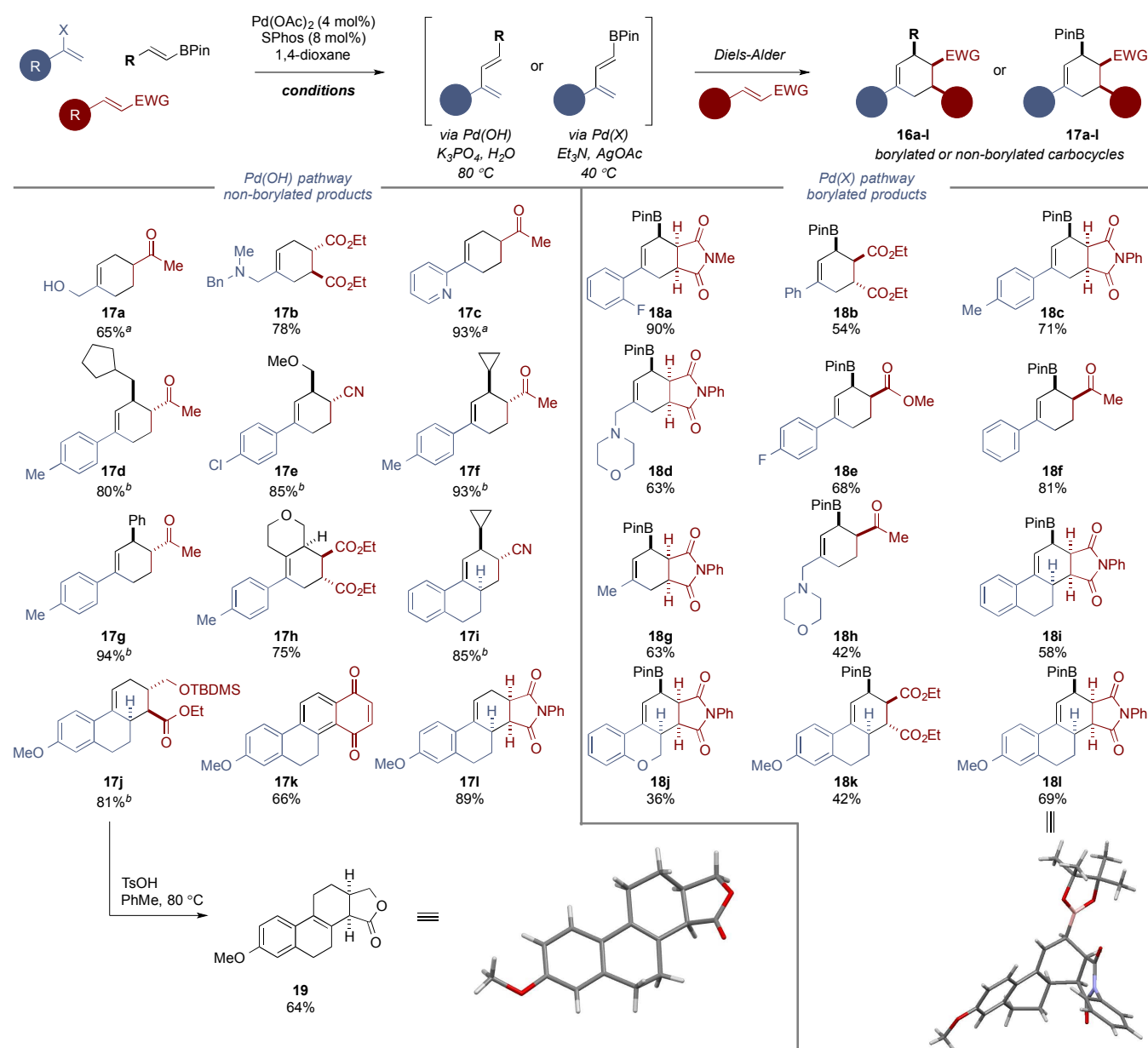
Base-mediated hydrolysis of vinyl BPIn could potentially explain some of the discrepancies observed. However, analysis of

styrenyl BPin with a series of bases at 80 °C revealed no hydrolysis: the vinyl BPin remained intact with some small levels of protodeboronation observed for KOH (see SI).¹⁹

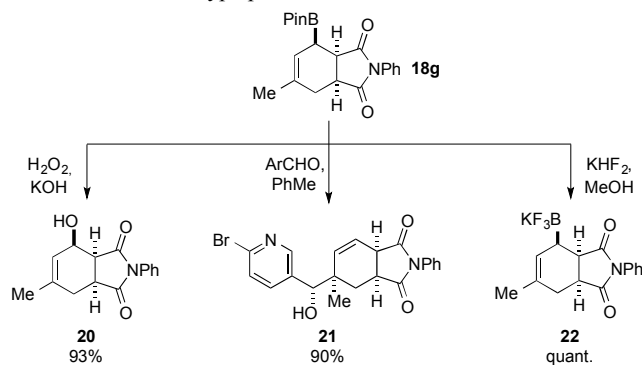
As shown above, a change in reaction medium is sufficient to induce significant changes to the product distribution, favoring Suzuki-Miyaura with inorganic bases (*e.g.*, K₃PO₄) and Mizoroki-Heck with Et₃N. Accordingly, we assessed the generality of this base-induced transmetalation switch across a range of aryl halides (I, Br, Cl) using the Pd(OAc)₂/SPhos system (Scheme 5). The switch took place with complete fidelity, delivering the orthogonal products exclusively and in generally good yield. Some diminished Heck efficiency was noted with substrates containing Lewis basic functionality, consistent with previous observations.¹¹ Interestingly, Mizoroki-Heck using Buchwald-type ligands is rare but was found to be effective under these conditions.^{20,21}

With control at Pd(II) established under catalytically-relevant conditions, we sought to demonstrate the utility of the transmetalation switch in a synthetic context. Inspired by cascade method-

ology used in natural product synthesis,²² we designed a three-component annulation reaction via cross-coupling of a vinylhalide/pseudohalide with a vinylBPin reagent to generate a diene intermediate. This diene would then engage a third olefin in a Diels-Alder reaction to produce the expected carbocyclic products. Importantly, this would be a divergent platform: control of Pd(II) using the knowledge garnered above would allow selective Mizoroki-Heck or Suzuki-Miyaura in the initial step, delivering borylated or non-borylated diene intermediates, and therefore borylated or non-borylated carbocycles (Scheme 6). In the event, the orthogonal series of products were generated in good yield via either pathway using a standard catalyst system (Pd(OAc)₂, SPhos) with K₃PO₄ driving Suzuki-Miyaura and Et₃N driving Mizoroki-Heck selectivity as expected. Use of AgOAc was found to improve the efficiency of the Mizoroki-Heck process with these olefinic electrophiles; this did not affect the selectivity profiles but bolstered reactivity, consistent with previous observations.¹⁰



Variation of the three olefinic components was broadly applicable allowing the preparation of functionalized mono- (**17a-g**; **18b,e,f,h**), bi- (**17h**; **18a,c,d,g**), tri- (**17i,j**; **18k**), and tetracyclic (**17k,l**; **18i,j,l**) products. Of particular note was the access to steroid-like scaffolds bearing a BPIn functional group (**18i,j,l**), allowing straightforward functionalization of the boron-bearing carbon and allylic position *via* established methods (Scheme 7).²³ For example, Brown oxidation (**20**), conversion of BPIn to BF₃K (to allow established cross-coupling methods at either position (**22**),²⁴ and nucleophilic allylation with carbonyl groups to deliver the Vaultier-Hoffmann-type product **21**.²⁵



Scheme 7. Derivatization of BPIn products.

In summary, using vinylBPIn as a bifunctional chemical probe, we have demonstrated that X→OH anion metathesis of (Ar)Pd(II) complexes can be controlled. In stoichiometric experiments, cross-coupling-relevant bases, co-solvent medium (solvent:H₂O composition), and temperature can be used to control the relative concentration of (Ar)Pd(II)(X) or (Ar)Pd(II)(OH) complexes. This allows control of cross-coupling pathways *via* promotion or inhibition of organoboron transmetalation, leading to either Suzuki-Miyaura or Mizoroki-Heck products on a bifunctional template. Finally, we show how this transmetalation switch can be used in a cascade cross-coupling/Diels-Alder annulation reaction, delivering (non)borylated carbocycles.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, NMR spectra, crystallographic data. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*allan.watson.100@strath.ac.uk

Funding Sources

No competing financial interests have been declared.

ACKNOWLEDGMENT

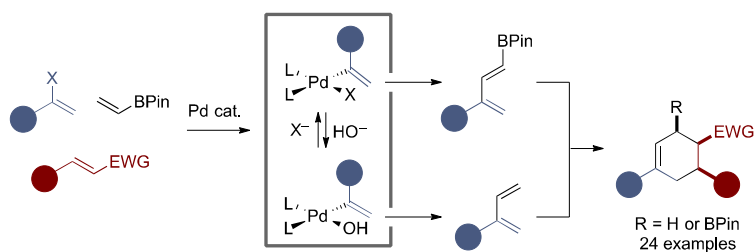
J.J.M thanks GlaxoSmithKline for a PhD studentship. C.P.S. thanks the Carnegie Trust for the Universities of Scotland for a PhD studentship. We thank the EPSRC UK National Mass Spectrometry Facility at Swansea University for analyses.

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Insert Table of Contents artwork here



- Base-controlled anion metathesis at Pd(II)
- Vinyl BPIn as a bifunctional chemical probe for Pd(II)(X) or Pd(II)(OH)
- Cascade cross-coupling/Diels-Alder \rightarrow (non)borylated carbocycles