

# A Journal of the Gesellschaft Deutscher Chemiker A Deutscher Chemiker GDCh International Edition www.angewandte.org

## **Accepted Article**

Title: Palladium-Catalysed C–H Bond Zincation of Arenes: Scope, Mechanism and the Role of Heterometallic Intermediates

Authors: Martí Garçon, Nicolette Wee Mun, Andrew J P White, and Mark Richard Crimmin

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.202014960

Link to VoR: https://doi.org/10.1002/anie.202014960

## WILEY-VCH

## **RESEARCH ARTICLE**

## Palladium-Catalysed C–H Bond Zincation of Arenes: Scope, Mechanism and the Role of Heterometallic Intermediates

Martí Garçon, Nicolette Wee Mun, Andrew J. P. White, Mark R. Crimmin\*<sup>[a]</sup>

[a] Martí Garçon, Nicolette Wee Mun, Dr. Andrew J. P. White, Dr. Mark R. Crimmin Molecular Sciences Research Hub, Imperial College London White City Campus, 82 Wood Lane, Shepherds Bush, London, W12 0BZ, UK E-mail: m.crimmin@imperial.ac.uk

Supporting information for this article is given via a link at the end of the document.

Abstract: Catalytic methods that transform C-H into C-X bonds are of paramount importance in synthesis. A particular focus has been the generation of organoboranes, organosilanes and organostannanes from simple hydrocarbons (X = B, Si, Sn). Despite the importance of organozinc compounds (X = Zn), their synthesis by the catalytic functionalisation of C-H bonds remains unknown. Here we show that a palladium catalyst and zinc-hydride reagent can be used to transform C-H into C-Zn bonds. The new catalytic C-H zincation protocol has been applied to a variety of arenes - including fluoroarenes, heteroarenes, and benzene - with high chemo- and regioselectivity. A mechanistic study shows that heterometallic Pd---Zn complexes play a key role in catalysis. The conclusions of this work are twofold; the first is that valuable organozinc compounds are finally accessible by catalytic C-H functionalisation, the second is that heterometallic complexes are intimately involved in bond-making and bond-breaking steps of C–H functionalisation.

#### Introduction

Catalytic methods to transform C-H bonds to C-C or C-X (X = heteroatom) bonds are an essential component of modern synthesis.<sup>[1],[2]</sup> Methods for C-H functionalisation can be applied on scale for upgrading simple hydrocarbons or more precisely in late-stage functionalisation of complex organic molecules and materials. Arguably, one of the most successful approaches in C-H functionalisation catalysis has been C-H borylation.<sup>[3]</sup> This reaction involves the transformation of C-H to C-B bonds and is typically catalysed by a transition metal complex.<sup>[4,5]</sup> The key advantage of C-H borylation is that it allows the preparation of boronic esters, compounds that find widespread use in synthesis due to their ease of handling and application in Suzuki-Miyaura cross-couplings. Related protocols involving the transformation of C-H bonds into C-Si and C-M bonds (M = Mg, Al, and Sn) have also been reported and are a powerful means to access potential partners for Hiyama, Kumada and Stille cross-coupling reactions.<sup>[6-11]</sup> Organozinc compounds, like organoboranes are widely applied in synthesis including Negishi couplings and are often versatile, mild and functional group tolerant partners. It is surprising then that a catalytic method for the transformation of C-H bonds into C-Zn bonds is unknown.

In this paper, we report the first catalytic method for the transformation of C–H to C–Zn bonds. The work complements modern approaches to C–H zincation which rely on specialist main group bases. For example, Knochel, Hevia, Mulvey and

others have developed families of mixed Zn/M (M = Mg, Li) bases to achieve the direct zincation of electron deficient arenes.<sup>[12–17]</sup> The current understanding of these systems is that both metals are crucial to reactivity.<sup>[18,19]</sup> As such these methods rely on a stoichiometric equivalent of an s-block metal. In contrast, the new catalytic method we report uses a palladium catalyst for C–H zincation. Our approach is highly efficient, forming only H<sub>2</sub> as a by-product. This reaction gives access to organozinc compounds which are robust, easy to handle and are active partners for Negishi cross-coupling reactions.

We have conducted a detailed analysis of the mechanism of C–H zincation, which shows that heterometallic complexes involving both Pd and Zn play a vital role in the catalytic cycle. We show for the first time that heterometallic Pd---Zn compounds can engage in a series of steps required for catalytic turnover (oxidative addition, ligand exchange, reductive coupling). While there is pioneering work demonstrating some of these steps in isolation, <sup>[20],[21]</sup> this is the first time they have been integrated into an efficient catalytic cycle.

#### **Results and Discussion**

Reaction Scope: The reaction of C<sub>6</sub>F<sub>5</sub>H and 1.1 – 1.2 equiv. of the  $\beta$ -diketiminate supported zinc hydride complex 1 in the presence of 2 mol% [Pd(PCy<sub>3</sub>)<sub>2</sub>] afforded 2a in excellent yield after 1 day at 50 °C. A control reaction between 1 and C<sub>6</sub>F<sub>5</sub>H gave only trace amounts of the product (<2%) after 3 days at 50 °C. In the absence of substrate and catalyst, 1 is thermally stable under reaction conditions. We believe the primary role of  $\beta$ -diketiminate ligand is to provide kinetic stability to this species and onward reaction intermediates. The reaction scope was investigated and a range of fluoroarenes and heteroarenes were amenable to C-H zincation forming 2a-t (Table 1 and 2). High chemoselectivity was observed despite the fact that [Pd(PCy<sub>3</sub>)<sub>2</sub>] is known to catalyse the functionalisation of C-F bonds of fluoroarenes.<sup>[22],[23]</sup> For fluoroarenes, the regiochemistry appears to be dictated by the ortho-fluorine effect, with substitution occurring at sites adjacent to at least one fluorine substituent. Similar trends have been observed in the C-H silvlation and borylation of these substrates.<sup>[8],[24],[25]</sup> For highly fluorinated substrates the reaction operates under mild conditions even when using the fluoroarene as the limiting reagent.<sup>[26]</sup> Halogen, trifluoromethyl, and methoxy functional groups are all tolerated.

#### **RESEARCH ARTICLE**



Arenes with lower fluorine content react slower. Using an excess of fluoroarene (10 equiv.), however, it was possible to achieve good yields for even the most challenging substrates. Under the optimised conditions, fluorobenzene ( $C_6H_5F$ ) only reacted sluggishly (<30 % conversion, 3d, 80 °C). The scope can even be expanded to the C–H zincation of benzene, provided the substrate is used as a solvent and the reaction is conducted under static vacuum to remove the H<sub>2</sub> by-product. Furthermore, the reaction scope is not limited to fluoroarenes. Heteroarenes were found to engage in these reactions under mild conditions and high selectivity. C–H zincation is observed to occur selectively at the 2-position of oxygen- and sulfur-containing heterocycles. In contrast, indoles favoured functionalisation at the 3-position. The products could be isolated cleanly despite the precedent for

related C–H alumination products to undergo ring-expansion reactions under similar conditions.  $^{\left[ 27\right] }$ 

Compounds **2a-t** could be crystallised from crude reaction mixtures and fully characterised by multinuclear NMR and IR spectroscopy, high-resolution mass spectrometry and single crystal X-ray diffraction. These products proved to be remarkably robust. In hydrocarbon solutions they can survive exposure to air for short periods of time (1.5 - 4 h) without decomposing. The solid-state structures of **2a-t** resemble known  $\beta$ -diketiminate supported zinc aryl complexes and do not warrant detailed comment.<sup>[28]</sup> Single crystal X-ray diffraction data show two main conformations based on the aryl ring existing either approximately coplanar or orthogonal to the plane created by the  $\beta$ -diketiminate ligand (see SI for details).

## **RESEARCH ARTICLE**



Curious as to the mechanism of C–H zincation catalysed by  $[Pd(PCy_3)_2]$ , we undertook a series of stoichiometric experiments between the different components of the reaction. These experiments unveiled several reactions of direct relevance to catalysis. This information, in combination with DFT calculations, was used to build a mechanistic and kinetic model which was further interrogated through kinetics experiments. We detail these findings below.

**Coordination of \sigma(Zn–H) Bonds to Pd:** The reaction between 1 and [Pd(PCy<sub>3</sub>)<sub>2</sub>] allowed the identification of the reversible binding of the zinc hydride to the catalyst. 1 and [Pd(PCy<sub>3</sub>)<sub>2</sub>] react to form the bis( $\sigma$ -zincane) complex [Pd(PCy<sub>3</sub>)(1)<sub>2</sub>] (3a) and PCy<sub>3</sub> at 253 K. At 193 K, [Pd(PCy<sub>3</sub>)<sub>3</sub>] could also be identified as part of this reaction mixture.<sup>[29]</sup> This reaction is reversible and the equilibrium is completely displaced towards the starting materials at 298 K. At 233 K, 3a demonstrates a characteristic resonance at  $\delta$  = 29.3 ppm in the <sup>31</sup>P NMR spectrum.

Although **3a** could not be isolated, the reaction of 2 equiv. of **1** with [Pt(PCy<sub>3</sub>)<sub>2</sub>] allowed isolation of **3b**, a direct platinum analogue (Figure 1b). **3b** is stable at 298 K in hydrocarbon solutions and demonstrates diagnostic resonances at  $\delta = -4.97$  ppm, 39.4 ppm and -5797 ppm in the <sup>1</sup>H-, <sup>31</sup>P- and <sup>195</sup>Pt-NMR, respectively. The hydride resonance appears as a doublet (<sup>2</sup>*J*<sub>P-H</sub> = 7.7 Hz) and has clearly resolved Pt satellites (<sup>1</sup>*J*<sub>PLH</sub> = 719 Hz). The <sup>195</sup>Pt NMR spectrum is resolved into a doublet of triplets (<sup>1</sup>*J*<sub>PLP</sub> = 2516 Hz,

 ${}^{1}J_{\text{Pt-H}} = 719 \text{ Hz}$ ) allowing unambiguous assignment of the number of hydride ligands on Pt. In the infrared spectrum, a stretch at 1708 cm<sup>-1</sup> is assigned to a v(Pt-H) vibration. The structure of **3b** was determined by single crystal X-ray diffraction (Figure 1d). While the position of the hydride ligands could not be located from the Fourier difference map, they almost certainly lie in the plane of the molecule, *trans* disposed to one another, forming a Tshaped motif with Pt and the PCy<sub>3</sub> ligand. A closely related magnesium analogue of **3b** has been reported by our group and the hydride locations of this complex have been confirmed by neutron diffraction.<sup>[30]</sup> The Pt–Zn distances of **3b** of 2.4816(6) and 2.4848(7) Å are close to the sum of the covalent radii (Pyykkö, 2.41 Å; Pauling, 2.54 Å; Alvarez, 2.58 Å).<sup>[31–33]</sup> The Pt–P distance of 2.316(1) Å is unremarkable.

Considering the stepwise ligand substitution of  $[M(PCy_3)_2]$  (M = Pd, Pt) to form **3a-b**, it is likely that the first step involves association of 1 equiv. of **1** to form a 3-coordinate, 16-electron  $\sigma$ -zincane complex. Reaction of 2 equiv. of **1** with  $[Pd(dcpe)]_2$  (dcpe = bis(dicyclohexylphosphino)ethane) supports this hypothesis and allows the isolation of **4**, a  $\sigma$ -zincane complex bearing a chelating diphosphine ligand (Figure 1c). **4** is characterised by a <sup>1</sup>H resonance at  $\delta$  = -0.80 ppm (t, <sup>2</sup>J<sub>P-H</sub> = 56 Hz) and a single <sup>31</sup>P NMR resonance at  $\delta$  = 52.8 ppm. A single crystal X-ray diffraction experiment on **4** reveals a Pd–Zn distance of 2.4499(7) Å that is again close to the sum of the covalent radii (Pyykkö, 2.38 Å; Pauling, 2.53 Å; Alvarez, 2.61 Å).<sup>[34]</sup>

#### **RESEARCH ARTICLE**



Figure 1. Reaction of 1 with (a) [Pd(PCy<sub>3</sub>)<sub>2</sub>], (b) [Pt(PCy<sub>3</sub>)<sub>2</sub>], and (c) [Pd(dcpe)]<sub>2</sub>. (d) Crystal structures of 3b and 4.

The Pd–H and Zn–H distances of 1.59(4) and 1.79(3) Å and the Pd–H–Zn angle of 93° are consistent with the description of this complex as a  $\sigma$ -zincane complex.<sup>[35]</sup> The Pd–P distances are slightly asymmetric, taking values of 2.3382(8) and 2.287(1) Å respectively, with that *trans* to the hydride moiety being longer (Figure 1d).<sup>[36]</sup>

The bonding in **3b** and **4** was interrogated with DFT calculations. The bonding in complex **4** is consistent with that of a  $\sigma$ -complex; NBO analysis shows donation from the  $\sigma$ -(Zn–H) orbital into an empty Pd orbital and backdonation of a filled Pd d-orbital into the  $\sigma^*$ -(Zn–H) orbital, as the most characteristic bonding features of this complex. The bonding in **3b** was more complex. We have characterised in detail a number of compounds involving Zn–H bonds coordinated to transition metals;<sup>[35],[37]</sup> and the Zn–-H distances typically range from ~ 1.7 to 2.2 Å. The Zn–--H distance in **3b** was calculated to be 1.9 Å. These data, in combination with Wiberg Bond Indices, indicate that **3b** contains stretched Zn–--H bonds (see Supporting Information). In combination, these experiments demonstrate the reversible binding of the Zn–H bond of **1** to Pd. This binding event plays an important role in both oncycle and off-cycle steps during catalysis (*vide infra*).

**Oxidative Addition:** Based on their facile formation and ease of ligand exchange, Pd---Zn heterometallic complexes likely play a key role in catalytic C--H zincation. To interrogate this idea further, reactions between the substrate  $C_6F_5H$  and the Pd and Pt complexes described above were undertaken. These experiments were designed to probe the key C--H bond breaking step; the oxidative addition to M(0) (M = Pd, Pt). For partially fluorinated substrates, chemoselectivity for C--H or C--F bond functionalisation becomes an important consideration.<sup>[38]</sup>

A stoichiometric reaction between [Pd(PCy<sub>3</sub>)<sub>2</sub>] and C<sub>6</sub>F<sub>5</sub>H revealed trace amounts of trans-[Pd(PCy<sub>3</sub>)<sub>2</sub>(F)(p-C<sub>6</sub>F<sub>4</sub>H)] derived from the oxidative addition of the C–F bond to  $\mathsf{Pd}(0).^{[39],[40]}$  There was no spectroscopic evidence for trans-[Pd(PCy<sub>3</sub>)<sub>2</sub>(H)(C<sub>6</sub>F<sub>5</sub>)] formed from oxidative addition of the C-H bond. In contrast, the reaction of the heterometallic Pt---Zn complex 3b with C6F5H allowed the identification of the C-H oxidative addition product (Figure 2b). The reaction of 3b with 5 equiv. of C<sub>6</sub>F<sub>5</sub>H at 60 °C for 3 h gave a mixture of products including platinum complex 5, fluoroarenes derived from the hydrodefluorination of C<sub>6</sub>F<sub>5</sub>H and a zinc compound assumed to be the fluoride analogue of 1. Fractional crystallisation resulted in isolation of a few single crystals of 5. 5 can be viewed as a Pt(II) complex bearing a phosphine ligand and hydrides that bridge to a zinc center. Diagnostic resonances are observed in the <sup>1</sup>H-NMR spectrum at  $\delta_{\text{H-trans}}$  = -7.59 ppm (<sup>1</sup>J<sub>H-Pt</sub> = 581 Hz - satellites) and  $\delta_{\text{H-cis}}$  = -4.39 ppm (dd,  ${}^{2}J_{H-P}$  = 113 Hz,  ${}^{2}J_{H-H}$  = 6.5 Hz,  ${}^{1}J_{H-Pt}$  = 671 Hz satellites) and the <sup>31</sup>P-{<sup>1</sup>H}-NMR spectrum at  $\delta$  = 30.9 ppm (<sup>1</sup>J<sub>P-Pt</sub> = 2877 Hz). In the solid-state, 5 adopts a geometry that is approximately square planar at platinum and tetrahedral at zinc. The hydride and  $\sigma$ -zincane ligands organise themselves in a *cis* arrangement such that both hydrides can interact and bridge between both metal centres. The Pt---Zn distance of 2.5184(8) Å is similar to those recorded for 3b. The Pt-C bond length of 2.067(4) Å is consistent with known Pt(II) fluoroaryl complexes,[41] while the C---H1 separation is ~2.5 Å. The Pt-H and Zn-H distances are similar across both hydride positions, and these take values of 1.59(4), 1.66(6), 1.81(4) and 1.78(5) Å for Pt-H1, Pt-H2, Zn-H1 and Zn-H2 respectively.

#### **RESEARCH ARTICLE**



Figure 2. Reaction of  $C_6F_5H$  with (a)  $[Pd(PCy_3)_2]$  and (b) 3b. (c) Crystal structure of 5.

Based on the current understanding, we suggest that the oxidative addition of both the C–H and C–F bonds of  $C_6F_5H$  to Pd(0) may be reversible (SI, Figure S23).<sup>[40]</sup> Unique insight into the C–H oxidative addition step could be gained by trapping an analogue of the C–H oxidative addition product as a heterometallic Pt---Zn complex.

DFT Calculations: To better understand the mechanism of catalytic C-H zincation, a series of DFT calculations  $(\omega B97x/BS1)^{[42]}$  were undertaken (see SI for details). A low energy pathway was identified involving Pd---Zn heterometallic complexes. Specifically, [Pd(PCy<sub>3</sub>)(1)] was identified as a key catalytic intermediate. The reaction sequence is initiated by the oxidative addition of the C-H bond of C<sub>6</sub>F<sub>5</sub>H to this 14-electron Pd(0) intermediate (see SI for alternative pathways).<sup>[43],[10]</sup> From [Pd(PCy<sub>3</sub>)(1)] and C<sub>6</sub>F<sub>5</sub>H, formation of Int-1, a weakly associated complex of the fluoroarene and active catalyst, is mildly exergonic. Oxidative addition occurs through **TS-1** ( $\Delta G^{\ddagger} = +1.9 \text{ kcal mol}^{-1}$ ) and is expected to reversibly form Int-2 based on the extremely low barrier for the forward reaction and modest stabilisation of the product ( $\Delta G^{\circ}_{298K} = -7.8$  kcal mol<sup>-1</sup>). **Int-2** is a direct isostructural analogue of the crystallographically characterised complex 5. TS-1 involves a 3-centered Pd···H···C interaction and population of the  $\sigma^*$ -orbital of the C–H bond of the fluoroarene with electrons from a d-orbital of Pd. This transition state is palladium centred.

Despite the relocation of the hydrogen atom to a bridging hydride in **Int-2**, the Zn atom does not interact directly with the hydrogen atom in **TS-1** and it would not be accurate to classify this reaction as a 4-centered ligand-assisted oxidative addition.<sup>[44–46]</sup>

A ligand exchange reaction of a further equivalent of 1 with Int-2 forms Int-3. A subsequent concerted rearrangement of this complex forms Int-4 which contains both 2a and H<sub>2</sub> within the coordination sphere of Pd. TS-2 involves the reorganisation of electron density between the equatorial ligands of palladium. Simultaneous migration of the perfluorinated  $\sigma$ -aryl ligand from Pd to Zn is accompanied by reductive coupling of the hydride ligands.<sup>[21]</sup> This concerted process involves a reduction in the formal oxidation state at the transition metal from Pd(II) back to Pd(0). The catalytic cycle is closed by further ligand exchange reactions of Int-4 by coordination of PCy3 and liberation of dihydrogen and 2a to reform [Pd(PCy<sub>3</sub>)(1)]. Overall the C-H zincation reaction is slightly exergonic ( $\Delta G^{\circ}_{298K} = -1.4$  kcal mol<sup>-1</sup>). The pathway predicts that C-H activation should be fast and reversible while the C-H functionalisation (formation of the C-Zn bond) is slow. The calculated Gibbs activation energy required for catalyst turnover is  $\Delta G^{\ddagger} = 23.0$  kcal mol<sup>-1</sup>.



Figure 3. DFT calculated reaction pathway for catalytic C-H zincation.

#### **RESEARCH ARTICLE**



Figure 4. (a) Catalytic cycle. (b) Kinetic model and rate law (derived from steady-state approximation).

Catalytic Cycle, Kinetic Model and Kinetics: Based on the combination of the stoichiometric experiments and the DFT calculations a comprehensive catalytic cycle can be proposed (Figure 4a). A simpler catalytic cycle involving monometallic palladium complexes can be excluded based on not only the facile formation of Pd---Zn heterometallics, but also as independently prepared trans-[Pd(PCy<sub>3</sub>)<sub>2</sub>(H)(4-C<sub>5</sub>F<sub>4</sub>N)] was not catalytically competent (see SI). The pre-catalyst equilibria are off-cycle events, while the on-cycle species all involve Pd---Zn heterometallic complexes. Considering the most important offcycle equilibria and approximating the transformation of Int-2 to products by TS-2 as a single kinetically relevant non-reversible step, the kinetic model in Figure 4b can be derived. The associated rate law determined using the steady state approximation predicts complex kinetic behaviour but broadly suggests that the reaction should be 1st order in catalyst, partial order (0 to 1) in fluoroarene, and variable order in 1.<sup>[47]</sup> It is clear from this analysis that 1 can potentially act as an inhibitor of catalytic turnover.

To interrogate the model a series of kinetics experiments were undertaken. The reaction between 1 and  $C_6F_5H$  with  $[Pd(PCy_3)_2]$  as catalyst in  $C_6H_6$  was investigated. Under pseudo-first order conditions, the reaction was found to be 1<sup>st</sup> order in catalyst (see SI, Figure S29). At high conversion the data sets for In[1] versus time show slight deviation from linearity (Figure 5a). Initial rate methods were used to determine the orders in 1 and  $C_6F_5H$ . The

plot of  $ln[C_6F_5H]$  versus  $ln(v_{initial})$  gave an order in  $C_6F_5H$  of 0.6 consistent with the partial order predicted by the kinetic model (Figure 5b). A similar approach was used to determine the order in 1 and complex behaviour was revealed (Figure 5c). Two regimes were apparent. At low initial concentrations, Vinitial increases with increasing concentration of 1. This reaches a maximum however and further increasing the [1]initial leads to vinitial becoming smaller with increasing [1]initial. These results indicate that the order in 1 changes when changing the concentration of 1; this is not a simple case of saturation kinetics. In combination with curvature of the plots of ln[1] versus time away from a linear fit at high conversion (>2 half-lives), the proposed catalytic cycle, and derived kinetic model, the finding suggests that while 1 is involved in the turnover limiting step it also acts as an inhibitor of catalysis. At low [1]<sub>initial</sub> the reaction runs in a regime with weak catalytic inhibition and a hence a partial positive order is obtained for [1], whereas at high [1]initial catalyst inhibition becomes a dominant effect and a negative order is obtained for [1].

An Eyring analysis provided the activation parameters of the reaction,  $\Delta H^{\ddagger} = 16.8 \pm 1.1 \text{ kcal mol}^{-1}, \Delta S^{\ddagger} = -22 \pm 4 \text{ cal mol}^{-1} \cdot \text{K}^{-1}$ . These values provide a reasonable barrier for a reaction that occurs at 298 K,  $\Delta G^{\ddagger} = 23.3 \pm 2.2 \text{ kcal} \cdot \text{mol}^{-1}$ , which is in excellent agreement with that predicted by DFT calculations on the proposed pathway of  $\Delta G^{\ddagger} = 23.0 \text{ kcal mol}^{-1}$ .

### **RESEARCH ARTICLE**



Figure 5. Plots of (a) ln([10]-[2a]] vs. time with a linear fit over 2 half-lives and evidence of substrate inhibition at high conversions. (b) partial order in [ArH] from initial rates. (c) variable order in [1] from initial rates. (d) Eyring analysis.

A Hammett analysis was undertaken by performing experiments with para-substituted tetrafluorobenzenes (C<sub>6</sub>F<sub>4</sub>HR, R = F, H, Me, OMe, CI) under pseudo-first order conditions. Although there was not a quantitative correlation between the  $k_{obs}$  and Hammett  $\sigma$ parameters,<sup>[48]</sup> there was a clear trend that showed reaction acceleration with electron-withdrawing groups and deceleration with electron-donating groups on the para position of the fluoroarene (see SI for details). This trend likely arises due to a stabilisation of the accumulating negative charge on the fluoroaryl group and is consistent with a turnover-limiting catalytic sequence involving migration of the fluoroaryl ligand from the less electropositive Pd site to the more electropositive Zn site in TS-2.

While hindered by H/D exchange, a significant KIE could be observed for the reaction,  $k_H/k_D \sim 2.5$  to 3.5. These values are small compared to those arising from non-reversible oxidative addition of a C-H bond to a transition metal on the turnover limiting step.<sup>[10]</sup> Rather based on the mechanistic proposal, the KIE can be qualitatively assigned to a combination of an equilibrium isotope effect originating from the reversible oxidative addition of the C-H bond to Pd, and a KIE resulting from the subsequent steps that lead to C-H zincation.[49],[50]

Synthetic Application of Organozinc Complexes: The products of C-H zincation possess reactive C-Zn bonds with enormous potential in synthesis.<sup>[51]</sup> In order to showcase this, their performance as coupling partners in C-C bond formation reactions was investigated. 2a undergoes Negishi cross-coupling reactions in high yields under mild conditions. Preliminary reactions with a series of aryl bromides and aryl chlorides resulted in high yield (determined by <sup>19</sup>F-NMR spectroscopy) of the biaryl products (71-100%), using [Pd(PCy<sub>3</sub>)<sub>2</sub>] as a catalyst. The reaction could be conducted either from the isolated organozinc intermediates or in a one-pot procedure from 1 and the corresponding fluoroarene (see SI for details). While the resulting products can be prepared by other well-established methodologies,[52-55] these reactions importantly show that these organozinc compounds can engage in onwards chemistry and act as a point of synthetic diversification. In this regard, 2a was also found to engage in allylation reactions<sup>[56]</sup> through catalytic palladium  $\pi$ -allyl intermediates (see SI for further details).

#### Conclusions

In summary, we report a new catalytic reaction for the transformation of C-H bonds to C-Zn bonds. Catalytic C-H zincation has been achieved for a wide variety of arenes with high

Mulvey, Chem. Commun. 2008, 2638-2640.

F. M. Miloserdov, N. A. Rajabi, J. P. Lowe, M. F. Mahon, S. A.

Macgregor, M. K. Whittlesey, J. Am. Chem. Soc. 2020, 142, 6340-

M. Chen, S. Jiang, L. Maron, X. Xu, Dalton Trans. 2019, 48, 1931-

D. Breyer, T. Braun, A. Penner, Dalton Trans. 2010, 39, 7513-7520.

T. P. Pabst, J. V. Obligacion, É. Rochette, I. Pappas, P. J. Chirik, J.

J. Takaya, S. Ito, H. Nomoto, N. Saito, N. Kirai, N. Iwasawa, Chem.

P. Wedi, M. van Gemmeren, Angew. Chem. Int. Ed. 2018, 57,

T. N. Hooper, R. K. Brown, F. Rekhroukh, M. Garçon, A. J. P.

White, P. J. Costa, M. R. Crimmin, Chem. Sci. 2020, 11, 7850-

K. Pang, Y. Rong, G. Parkin, Polyhedron 2010, 29, 1881-1890.

F. Barrios-Landeros, B. P. Carrow, J. F. Hartwig, J. Am. Chem. Soc.

W. Chen, T. N. Hooper, J. Ng, A. J. P. White, M. R. Crimmin,

Angew. Chem. Int. Ed. 2017, 56, 12687-12691.

Am. Chem. Soc. 2019, 141, 15378–15389.

Commun. 2015, 51, 17662-17665.

[20]

[21]

[22]

[23]

[24]

[25]

[26]

[27]

[28] [29] 6349.

1935

13016-13027.

2009, 131, 8141-8154.

7857.

#### WILEY-VCH

### **RESEARCH ARTICLE**

efficiency and selectivity. The reaction mechanism has been interrogated and heterometallic complexes identified as key intermediates. The new catalytic reaction not only provides access to high-value organozinc compounds for use in synthesis, it also showcases a remarkable role for heterometallic complexes and metal---metal cooperativity in the catalytic functionalisation of C-H bonds. Heterometallic cooperativity is an emerging design approach in catalysis. The mechanistic insight we provide has the potential to inspire further studies and provides a unique perspective on transmetallation events involving Pd and Zn.[57],[58]

#### Acknowledgements

We are grateful to the European Research Council (FluoroFix:677367) and the Royal Society (UF090149). Johnson Matthey are thanked for generous donation of PdCl<sub>2</sub>. Pete Haycock is gratefully acknowledged for assistance with NMR spectroscopy. M.G. thanks "la Caixa" Foundation (ID 100010434) for a postgraduate scholarship (LCF/BQ/EU19/11710077).

Keywords: C-H Zincation • C-H activation • Palladium •

Refere		[24]	D. Diadde M. Ataumi Cham. Fur. 1 2000 45 496 407
кејеје	Deferences		P. Pyykko, M. Alsumi, <i>Chem. Eur. J.</i> <b>2009</b> , 75, 166–197.
References		[33]	B. Cordero, V. Gómez, A. E. Platero-Prats, M. Revés, J. Echeverría,
.1] I	R. G. Bergman, Nature 2007, 446, 391–393.		E. Cremades, F. Barragán, S. Alvarez, Dalton Trans. 2008, 2832-
	R. H. Crabtree, J. Chem. Soc., Dalton Trans. 2001, 2437–2450.		2838.
 31 I	I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F.	[34]	A single crystal X-ray diffraction experiment showed there to be two
	Hartwig, Chem. Rev. 2010, 110, 890–931.		independent molecules within the unit cell of 4. There are no
[4]	G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice,		significant differences between the metrics of the two. Data are
	E. G. Robins, W. R. Roper, G. R. Whittell, L. J. Wright, Chem. Rev.		discussed for molecule A.
	1998, 98, 2685–2722.	[35]	O. Ekkert, A. J. P. White, M. R. Crimmin, Angew. Chem. Int. Ed.
[5]	S. Aldridge, D. L. Coombs, Coord. Chem. Rev. 2004, 248, 535–559.		<b>2016</b> , <i>55</i> , 16031–16034.
[6]	J. F. Hartwig, Acc. Chem. Res. 2012, 45, 864–873.	[36]	N. Nakata, S. Fukazawa, N. Kato, A. Ishii, Organometallics 2011,
[7]	C. Cheng, J. F. Hartwig, J. Am. Chem. Soc. 2015, 137, 592–595.		30, 4490–4493.
[8] I	M. R. Elsby, S. A. Johnson, <i>J. Am. Chem. Soc.</i> <b>2017</b> , <i>139</i> , 9401–9407.	[37]	O. Ekkert, A. J. P. White, M. R. Crimmin, <i>Chem. Eur. J.</i> <b>2017</b> , <i>23</i> , 5682–5686.
9] I	M. E. Doster, J. A. Hatnean, T. Jeftic, S. Modi, S. A. Johnson, J.	[38]	O. Eisenstein, J. Milani, R. N. Perutz, Chem. Rev. 2017, 117, 8710-
	Am. Chem. Soc. 2010, 132, 11923–11925.		8753.
10] .	T. N. Hooper, M. Garcon, A. J. P. White, M. R. Crimmin, Chem. Sci.	[39]	N. A. Jasim, R. N. Perutz, A. C. Whitwood, T. Braun, J. Izundu, B.
	2018, 9, 5435–5440.		Neumann, S. Rothfeld, HG. Stammler, Organometallics 2004, 23,
[11]	M. Garçon, A. J. P. White, M. R. Crimmin, Chem. Commun. 2018,		6140–6149.
	54, 12326–12328.	[40]	S. A. Macgregor, D. C. Roe, W. J. Marshall, K. M. Bloch, V. I.
[12]	S. H. Wunderlich, P. Knochel, Angew. Chem. Int. Ed. 2007, 46,		Bakhmutov, V. V. Grushin, J. Am. Chem. Soc. 2005, 127, 15304-
-	7685–7688.		15321.
[13]	M. Mosrin, P. Knochel, Org. Lett. 2009, 11, 1837–1840.	[41]	R. P. Hughes, A. J. Ward, J. A. Golen, C. D. Incarvito, A. L.
[14]	M. R. Becker, P. Knochel, Org. Lett. 2016, 18, 1462–1465.		Rheingold, L. N. Zakharov, Dalton Trans. 2004, 2720–2727.
[15]	C. I. Stathakis, S. M. Manolikakes, P. Knochel, Org. Lett. 2013, 15,	[42]	M. Garçon, A. J. P. White, M. R. Crimmin, Chem. Commun. 2018,
	1302–1305.		54, 12326–12328.
[16] I	L. Klier, D. S. Ziegler, R. Rahimoff, M. Mosrin, P. Knochel, Org.	[43]	L. P. Wolters, R. Koekkoek, F. M. Bickelhaupt, ACS Catal. 2015, 5,
1	Process Res. Dev. <b>2017</b> , <i>21</i> , 660–663.		5766–5775.
[17]	T. Bresser, M. Mosrin, G. Monzon, P. Knochel, J. Org. Chem. 2010,	[44]	S. Erhardt, S. A. Macgregor, J. Am. Chem. Soc. 2008, 130, 15490-
	75, 4686–4695.		15498.
18]	B. Conway, E. Hevia, A. R. Kennedy, R. E. Mulvey, Chem.	[45]	A. Nova, S. Erhardt, N. A. Jasim, R. N. Perutz, S. A. Macgregor, J.
	Commun. <b>2007</b> , 2864–2866.		E. McGrady, A. C. Whitwood, J. Am. Chem. Soc. 2008, 130, 15499-
[19] I	B. Conway, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E.		15511.

## **RESEARCH ARTICLE**

- [46] A. L. Raza, J. A. Panetier, M. Teltewskoi, S. A. Macgregor, T.Braun, Organometallics 2013, 32, 3795–3807.
- [47] J. Burés, Angew. Chem. Int. Ed. 2016, 55, 2028–2031.
- [48] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
- [49] G. Zhu, K. E. Janak, G. Parkin, *Chem. Commun.* **2006**, 2501–2503.
- [50] K. E. Janak, G. Parkin, *Organometallics* 2003, *22*, 4378–4380.
  [51] Y. Okamoto, K. Yoshioka, T. Yamana, H. Mori, *J. Organomet.*
- Chem. 1989, 369, 285–290.
- [52] M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, J. Am. Chem. Soc. 2006, 128, 8754–8756.
- [53] Z.-J. Luo, H.-Y. Zhao, X. Zhang, Org. Lett. **2018**, *20*, 2543–2546.
- [54] M. Ohashi, R. Doi, S. Ogoshi, *Chem. Eur. J.* **2014**, *20*, 2040–2048.
- [55] Y. Nakamura, N. Yoshikai, L. Ilies, E. Nakamura, Org. Lett. 2012, 14, 3316–3319.
- [56] S. Fan, F. Chen, X. Zhang, Angew. Chem. Int. Ed. 2011, 50, 5918– 5923.
- [57] R. J. Oeschger, P. Chen, Organometallics 2017, 36, 1465–1468.
- [58] M. García-Melchor, B. Fuentes, A. Lledós, J. A. Casares, G.
  Ujaque, P. Espinet, *J. Am. Chem. Soc.* 2011, 133, 13519–13526.

## **RESEARCH ARTICLE**

#### Entry for the Table of Contents



Insert text for Table of Contents here. A palladium catalyst and zinc-hydride reagent can be used to transform C–H into C–Zn bonds. The reaction scope includes fluoroarenes, heteroarenes, and benzene. Heterometallic Pd---Zn complexes play a key role in catalysis.

Institute and/or researcher Twitter usernames: @crimmingroup