Ligand and solvent control of selectivity in the C-H activation of a pyridylimine-substituted 1-naphthalene; a combined synthetic and computational study

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Abstract: The pyridylimine-substituted 1-naphthalenes, 2-(1-C10H7)-6-(CR=N(2,6-i-Pr2C6H3))C5H3N (R = Me HHLMe, H HLMe), react with Na[PdCl4] in acetic acid at elevated temperature to afford either ortho-C-H activation activated (HLMe)PdCl2 (2ortho) or the unactivated adduct (HLMe)PdCl2 (1b). Alternatively, 1b and its ketimine analogue (HLMe)PdCl (1a), can be prepared by treating (MeCN)2PdCl2 with either HLMe or HLMe in chloroform at room temperature. Regio-selective ortho-C-H activation to form 2ortho can also be initiated by the thermolysis of 1a in acetic acid, while no reaction occurs under similar conditions with 1b. Interestingly, the C-H activation of HLMe to give 2ortho is found to be reversible with 100% deuteration of the peri-site occurring on reacting Na[PdCl4] with HLMe in acetic acid-d6. By contrast, heating 1a in toluene gives a 55:45 mixture of 2ortho and its peri-activated isomer 2peri. Pure 2peri can, however, be obtained either from (HLMe)PdOAc (3peri) by OAc/Cl exchange or by the sequential reactions of 1a with firstly silver acetate then with aqueous sodium chloride. Intriguingly, a peri to ortho interconversion occurs on heating 2peri in acetic acid to give 2ortho. DFT calculations have been used to investigate the C-H activation steps and it is found that in acetic acid ortho-C-H activation is kinetically and thermodynamically favoured but peri-C-H activation is kinetically accessible (ΔΔG° = 2.4 kcal mol-1). By contrast in toluene, the reaction appears to be irreversible with the difference in barrier height for ortho- and peri-C-H activation very small within error of the method (ΔΔG° = 0.7 kcal mol-1), findings that are agreement with the empirically observed product distribution for 2ortho and 2peri. Single crystal X-ray structures are reported for 1a, 1b, 2ortho and 2peri.

Recently, metal ligating directing groups have been developed for the alternative activation of remote C-H bonds, including at the meta- and para-sites of an aromatic ring. Other factors have also been identified for the control of site-selectivity, including the innate reactivity of the substrate, the catalyst or metal-ligand combination and the solvent.

In recent years, we have been exploring the factors that influence site-selectivity in the C-H activation of a range of 1-substituted naphthalene molecules, in which we envisaged potential for both ortho- and peri-C-H activation. For example, reaction of the pyridylimine-containing 1-substituted naphthalene, 2-(1-C10H7)-6-(CMe=N(2,6-i-Pr2C6H3))C5H3N (HLMe), with Pd(OAc)2 led exclusively to peri-C-H activation of the naphthyl group, while for the pyridyl-alcohol analogue 2-(1-C10H7)-6-(CMeO2H)C5H3N solely the ortho-C-H activation product was observed (Scheme 1). DFT calculations were performed on the peri-pathway which revealed: (i) that the reaction proceeded by a mechanism commonly referred to as a concerted metatation deprotonation (CMD) or ambiphilic metal-ligand activation (AMLAA), involving an acetate ligand as an intramolecular base; (ii) that the peri-C-H activation was both kinetically and thermodynamically favoured; and (iii) that the site-selectivity of the C-H activation was controlled, in some measure, by the N,N-
bidentate directing group, since monodentate directing groups have a preference for the ortho-product. Indeed, the formation of the ortho-product (Scheme 1b) can be accounted for by assuming that the pyridine unit acts as monodentate directing ligand (c.f. ortho-palladation of 2-(1-naphthyl)pyridine), with the OH group coordinating during the final stages of the transformation.

Given this subtle balance between ortho- and peri-activation of a naphthalene ring, we decided to explore the reactivity of HLMe and its aldimine analogue, 2-(1-C10H7)-6-{CH=N(2,6-Me2-i-Pr)}2PhMeN (HLi), towards acetate-free palladium(II) sources and in particular the palladium(II) chlorides, (MeCN)2PdCl2 and Na2[PdCl4]. In these cases, the intramolecular base is now a chloride ligand rather than an κ1-acetate and as such a conventional CMD (or AMLA-6) type mechanism will be prevented.12

Full details of our synthetic investigation are disclosed with all key intermediates fully characterised. In addition, DFT calculations have been used to support the synthetic findings with a focus on determining the mechanism of C-H activation and the role of the chloride ligand and solvent on the selectivity of these reactions.

Results and discussion

(a) Synthesis and characterization

In the first instance we explored the reactivity of the tetrachloropalladate salt Na2[PdCl4] towards HLMe and HLi. Typically, the reactions were performed in acetic acid at 100 °C over extended reaction times. Using HLMe, precipitation of the adduct (HLMe)PdCl2 (1b) occurred after 24 hours while for HLi, the C-H activation product (Li)PdCl2 (2ortho) could be isolated in 85% yield after 48-60 hours (Scheme 2). Both 1b and 2ortho have been characterized by 1H/13C NMR and IR spectroscopy and mass spectrometry. In addition, both have been the subject of single crystal X-ray diffraction studies.

In the IR spectrum for 1b the ν(C=N)imine band is shifted by ca. 30 cm−1 to lower wavenumber compared to free HLi and consistent with effective coordination with the palladium centre. In the 1H NMR spectrum thirteen aromatic protons are evident indicating that no C-H activation has occurred; a singlet resonance at δ 8.28 can also be assigned to CH=N proton. In the aliphatic region two distinct septets and four doublets are seen for the isopropyl protons consistent with both restricted rotation about the Ar-CHMe2 bond and the inequivalent environment imposed on each isopropyl group by the positioning of the pendant naphthyl ring above or below the chelate ring. By contrast, in the 1H NMR spectrum of 2ortho, only 12 protons in the aromatic region could be detected confirming that C-H activation on the naphthyl moiety has been achieved. With the naphthyl group now coordinated to the palladium, the signals in the aliphatic region show a simpler pattern than in 1b with the two CH(Me)2 protons now taking the form of one septet while the CH(Me)2 protons are seen as only two doublets.

Single crystals of 1b and 2ortho were grown by slow diffusion of hexane into dichloromethane solutions containing the respective complex. The structures of 1b and 2ortho are different and will be discussed separately. A view of 1b is given in Figure 1; selected bond distances and angles are listed in Table 1. The structure consists of a palladium centre surrounded by two nitrogen donors belonging to the N,N-chelating pyridylimine and two monodentate chloride ligands to complete a distorted square planar geometry. The N(1)-Pd(1)-N(2) bite angle is 79.4(3)° which highlights the severe strain exerted by the naphthyl group on the imine bond. The two Pd-N distances show some variation with the one involving the pyridyl and imine units as well as a carbon derived from an ortho-activated naphthyl moiety.

A perspective view of 2ortho is shown in Figure 2; selected bond distances and angles are presented in Table 2. In this structure the palladium centre is bound by a tridentate N,N,C ligand and a single chloride ligand to form a geometry best described as distorted square planar. The N,N,C ligand makes use of the nitrogen donors from the pyridyl and imine units as well as a carbon derived from an ortho-activated naphthyl moiety. Two essentially planar five-membered chelate rings are formed with the metal centre with the exterior C-Pd distance notably shorter than the trans Nimine-Pd distance [Pd(1)-C(15) 1.960(7) vs. Pd(1)-N(1) 2.123(5) Å], likely reflecting the anionic nature of the former and the trans influence exerted by the naphthyl group on the imine.
It is assumed that due to the poor solubility of 1b in hot acetic acid, the subsequent ortho-palladation step was impeded. Hence, it would seem probable that a related dichloride species is involved as an intermediate in the formation of 2ortho, albeit not detectable. Accordingly, we treated HLMe with (MeCN)2PdCl2 in chloroform at room temperature affording (HLMe)2PdCl2 (1a) in high yield (Scheme 3); 1b could be prepared similarly.

Complex 1a has been characterised using the same techniques as that described for 1b and has been the subject of single crystal X-ray diffraction study (see ESI). Indeed, the structure of 1a shows similar structural features in the solid state to that for 1b adopting a distorted square planar geometry based on the N/N ligand and two chloride ligands (Figure S1). In solution, the key difference between 1b and 1a in the 1H NMR spectrum are the presence of a 3H singlet for the CMe=N protons in 1a and the absence of a downfield CH=N proton.

![Scheme 3. Stepwise route to 2ortho via 1a](image)

To confirm the role of dichloride complex 1a as an intermediate in the formation of 2ortho during the reaction of HLMe with Na2[PdCl4], we monitored the reaction of 1a by 1H NMR spectroscopy which showed the gradual consumption of 1a and the formation of 2ortho after 60 hours at 100 °C in acetic acid (Scheme 3), trace amounts (< 5%) of a second product, 2peri (vide infra), were also detectable. Needless to say, 1b due to its poor solubility in acetic acid, proved unreactive under similar reaction conditions.

With a view to targeting 2peri, the regio-isomer of 2ortho, we set about developing a viable synthetic route. Hence, treatment of 1a with two molar equivalents of silver acetate in chloroform gave a complex we tentatively assign as the C-H activation product [2-(1-C6H4-H)6-(CMe=N[2,6-i-Pr2C6H3])2Cl]Pd(OAc)2AgCl (3peri.AgCl), which on further reaction with aqueous sodium chloride gave 2peri in good yield (Scheme 4). Alternatively, 2peri could be obtained in comparable yield by a similar acetate-chloride exchange using pure 3peri previously prepared by the reaction of HLMe with Pd(OAc)2 in toluene.

In contrast to 1b, the palladium-nitrogen distance involving the central pyridine is now notably shorter than that to the imine [Pd(1)-N(2) 1.954(5) vs. Pd(1)-N(1) 2.123(5) Å], an observation presumably attributable to the constraints imposed by the tridentate ligand. The N-2,6-disopropylphenyl group adopts an orientation almost perpendicular to the imine vector (tors.: C(7)-N(1)-C(1)-C(2) 81.1°), while the C-N distance for the imine [1.283(7) Å] is typical of this functional group. On comparison with the three previously reported examples of crystallographically characterised ortho-palladated aryl-substituted pyridylimines, 2ortho displays comparable features.

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The precise structural identity of intermediate \( \text{Z}_{\text{peri}} \)-AgCl remains uncertain but the presence of 12 aromatic protons and only one acetate-Me is consistent with C-H activation having occurred. However, there is some variation of the chemical shift of the signals in the \(^1\)H NMR spectrum in CDCl\(_3\) when compared with \( \text{Z}_{\text{peri}} \), therefore we have ascribed this to adduct formation having occurred between \( \text{Z}_{\text{peri}} \) and the AgCl that is eliminated during the reaction.

Complex \( \text{Z}_{\text{peri}} \) has been characterised spectroscopically and has been subject of a single crystal X-ray diffraction study. Single crystals suitable for the study could be grown by slow diffusion of hexane into a dichloromethane solution of the complex. A perspective view of \( \text{Z}_{\text{peri}} \) is given in Figure 3; selected bond distances and angles are collected in Table 3. The structure resembles \( \text{Z}_{\text{ortho}} \) with a distorted square planar palladium centre bound by a \( N,N,C \) tridentate ligand along with a monodentate chloride ligand. The key difference in \( \text{Z}_{\text{peri}} \) is that the naphthyl moiety binds through the \( \text{peri} \)-carbon with the result that it is incorporated into a six-membered chelate ring. The larger ring system has the effect that the \( N_{\text{pyridine}}-\text{Pd-Cnaphthyl} \) bite angle of 94.14(11)° is more compatible with the geometrical requirements of the square planar geometry [c.f. 82.1(3)° in \( \text{Z}_{\text{ortho}} \)]. As with \( \text{Z}_{\text{ortho}} \) there are some consequent variations in the bond lengths between palladium and the donor atoms belonging to the \( N,N,C \) ligand with \( \text{Pd-N}_{\text{pyridine}}(2.104(2) \text{ Å}) > \text{Pd-Cnaphthyl}(1.987(3) \text{ Å}) \). In comparison with \( \text{Z}_{\text{ortho}} \) the \( \text{Pd-Cnaphthyl} \) distance is marginally longer in \( \text{Z}_{\text{peri}} \) [1.987(3) vs. 1.960(7) Å] with the effect that the \( \text{Pd-N}_{\text{pyridine}} \) Distance in \( \text{Z}_{\text{peri}} \) is relatively shorter [2.104(2) (\( \text{Z}_{\text{peri}} \)) vs. 2.123(5) Å (\( \text{Z}_{\text{ortho}} \))]. The N-aryl ring is again inclined close to perpendicular with respect to the imine vector [tors.: C(7)-N(1)-C(1)-C(2) 84.8°].

In the FAB mass spectrum of \( \text{Z}_{\text{peri}} \) a molecular ion peak as well as a fragmentation peak corresponding to the loss of a chlorine are evident. Like \( \text{Z}_{\text{ortho}} \), there are two inequivalent CHMe\(_2\)Me\(_2\) methyl groups at each ortho-site which manifests itself as two 6H doublets in the \(^1\)H NMR spectrum. The imine carbon is seen as the most downfield signal at \( \delta \) 171.2 in the \(^{13}\)C NMR spectrum while the imine methyl is visible as the most upfield signal at \( \delta \) 18.7.

(b) Mechanistic considerations

In contrast to our previous findings with \( \text{Pd(OAc)}_2 \),\(^{12}\) the selective formation of \( \text{Z}_{\text{ortho}} \) from either the reaction of \( \text{HLe}_{\text{o}} \) with \( \text{Na}_2[\text{PdCl}_4] \) in acetic acid at high temperature or by the thermolysis of \( 1\alpha \) in acetic acid raises some intriguing questions. For example, (i) are these transformations reversible, (ii) is the nature of the solvent important on the selectivity and (iii) does \( \text{Z}_{\text{peri}} \) convert to \( \text{Z}_{\text{ortho}} \) in acetic acid at high temperature?

To explore the reversibility of the C-H activation, we carried out a small scale reaction of \( \text{HLe}_{\text{o}} \) with \( \text{Na}_2[\text{PdCl}_4] \) in acetic acid-\( d_4 \) at 100 °C (Scheme 5, equation 1). Inspection of the \(^1\)H NMR spectrum revealed the formation of \( \text{Z}_{\text{ortho}} \) in which 100% deuteration at the peri-position had occurred (the corresponding proto-signal had disappeared, see SI). Therefore, this finding would suggest that this palladation reaction in acetic acid is reversible.

With a view to probing the role played by solvent on the selectivity of the C-H activation, we explored the thermolysis of \( 1\alpha \) in toluene, initially at 60 °C for 12 hours. At this temperature the reaction was incomplete, with 70% starting material still present but the sticking 30% comprised of an approximately equal mixture of \( \text{Z}_{\text{ortho}} \) and \( \text{Z}_{\text{peri}} \). However, on raising the temperature to 100 °C, full consumption of starting material was noted and the formation of a 55:45 mixture of \( \text{Z}_{\text{ortho}} \) and \( \text{Z}_{\text{peri}} \) was observable after 24 hours (Scheme 5, equation 2). Hence, it would seem apparent that the high selectivity for \( \text{Z}_{\text{ortho}} \) observed in acetic acid is affected by the choice of solvent.

Given the preference for \( \text{Z}_{\text{ortho}} \) when the C-H activation reactions were performed in acetic acid, it was of interest to establish if the isomer \( \text{Z}_{\text{peri}} \) would undergo conversion to \( \text{Z}_{\text{ortho}} \) on heating in acetic acid. Hence, monitoring a reaction of pure \( \text{Z}_{\text{peri}} \) at 100 °C in acetic acid revealed that after 60 hours greater than 90% conversion to \( \text{Z}_{\text{ortho}} \) was achieved (Scheme 5, equation 3). Likewise, taking the 55:45 mixture of \( \text{Z}_{\text{ortho}} \) and \( \text{Z}_{\text{peri}} \) that was obtained from the reaction in toluene, and heating it in acetic acid at 100 °C
Density functional theory (DFT) calculations were employed to further investigate the site-selectivity for the reaction of pyridyl-naphthalene \( \text{HL}_{\text{Me}} \) with \( \text{Na}_2[\text{PdCl}_4] \). The energies discussed in the main text are Gibbs energies that include both a dispersion correction and a solvent correction (\( \text{AcOH} \) or toluene).

First, we computed the structures of the two isomeric products \( \text{2}_{\text{ortho}} \) and \( \text{2}_{\text{peri}} \). The optimised structures are in accord with the solid-state structures obtained from single crystal X-ray diffraction. The computed solution energy of the \( \text{ortho} \)-isomer \( \text{2}_{\text{ortho}} \) was 1.2 kcal-mol\(^{-1}\) lower than that of the \( \text{peri} \)-isomer \( \text{2}_{\text{peri}} \) in acetic acid and 1.4 kcal-mol\(^{-1}\) lower in toluene. This difference in energies is consistent with the \( \text{ortho} \)-isomer \( \text{2}_{\text{ortho}} \) being the thermodynamic product of the C-H activation reaction.

Next, we investigated the kinetic barriers to the alternative \( \text{ortho} \)- and \( \text{peri} \)-C-H activations of the \( \text{PdCl}_2 \) complex \( 1\text{a} \). Whereas C-H activation mediated by palladium carboxylate complexes has been thoroughly investigated by computational methods,\(^{12} \) C-H activation by palladium chloride complexes has been less well studied.\(^{19} \) We have ruled out an acetic acid mediated L\( \text{PdCl}_2 \) transformation as (i) such conversions rely on salt elimination approaches, and (ii) if an acetate ligand was generated reaction mechanisms were investigated based on dichloride \( 1\text{a} \), including oxidative addition and concerted metatation-deprotonation (CMD or ambiphilic metal ligand activation, AMLa); for the CMD reaction, mechanisms involving both inner- and outer-sphere chloride were studied. The inner-sphere CMD mechanism, as shown in Figure 4, proved to be the lowest energy pathway for both the \( \text{ortho} \)- and \( \text{peri} \)-C-H activation of \( 1\text{a} \) (see ESI for a comparison of all the mechanisms investigated).

For the \( \text{ortho} \)-C-H activation of \( 1\text{a} \), a one-step reaction was found, involving the direct cleavage of the \( \text{ortho} \)-C-H bond and concomitant transfer of the H atom to the nearest chloride ligand (Figure 4). In contrast with the commonly observed CMD mechanism involving a metal \( \kappa^1\)-acetate, which has a 6-membered ring transition state, this reaction involving a palladium chloride has a 4-membered ring transition state. This CMD reaction proceeds via TS(\( 1\text{a-B}_{\text{ortho}} \)) \( \Delta G^\ddagger(\text{AcOH}) = 20.4 \text{ kcal-mol}^{-1} \); \( \Delta G^\ddagger(\text{PhMe}) = 21.3 \text{ kcal-mol}^{-1} \) to give the intermediate HCl complex \( \text{B}_{\text{ortho}} \) \( \Delta G(\text{AcOH}) = 6.5 \text{ kcal-mol}^{-1} \); \( \Delta G(\text{PhMe}) = 3.9 \text{ kcal-mol}^{-1} \); subsequent dissociation of HCl gives the product \( \text{2}_{\text{ortho}} \) \( \Delta G(\text{AcOH}) = -34.0 \text{ kcal-mol}^{-1} \); \( \Delta G(\text{PhMe}) = -36.0 \text{ kcal-mol}^{-1} \).

By contrast, for the \( \text{peri} \)-C-H activation of \( 1\text{a} \) a two-step reaction was found, involving a change in geometry at the metal prior to C-H cleavage (Figure 4). First, square planar complex \( 1\text{a} \) is transformed to intermediate A \( \Delta G(\text{AcOH}) = 16.4 \text{ kcal-mol}^{-1} \); \( \Delta G(\text{PhMe}) = 16.3 \text{ kcal-mol}^{-1} \), via TS(\( 1\text{a-A} \)) \( \Delta G^\ddagger(\text{AcOH}) = 22.8 \text{ kcal-mol}^{-1} \); \( \Delta G^\ddagger(\text{PhMe}) = 22.0 \text{ kcal-mol}^{-1} \). Intermediate A adopts a square-based pyramidal geometry, with an agostic \( \text{peri} \)-C-H interaction displacing the closest chloride ligand, which now occupies the apical site. The subsequent activation of the \( \text{peri} \)-C-H bond in A (also via a 4-membered ring transition state) is effectively a barrierless reaction: once the dispersion and solvent corrections have been applied to the gas phase free energy, the transition state TS(\( \text{A-B}_{\text{peri}} \)) is lower in energy than intermediate A \( \Delta G^\ddagger(\text{AcOH}) = 15.7 \text{ kcal-mol}^{-1} \); \( \Delta G^\ddagger(\text{PhMe}) = 16.2 \text{ kcal-mol}^{-1} \). The two transition states, TS(\( 1\text{a-A} \)) and TS(\( \text{A-B}_{\text{peri}} \)), are similar in structure; the major difference is a shorter Pd–Cl distance in TS(\( 1\text{a-A} \)), and a shorter Pd–C–H distance in TS(\( \text{A-B}_{\text{peri}} \)). Importantly, the first transition state, TS(\( 1\text{a-A} \)), is the highest energy point on the \( \text{peri} \)-C-H activation pathway. The direct product of the \( \text{peri} \)-C-H activation is also an HCl adduct, B\( _{\text{peri}} \) \( \Delta G(\text{AcOH}) = 7.7 \text{ kcal-mol}^{-1} \); \( \Delta G(\text{PhMe}) = 5.2 \text{ kcal-mol}^{-1} \); as with B\( _{\text{ortho}} \), dissociation of HCl then gives the product \( \text{2}_{\text{peri}} \) \( \Delta G(\text{AcOH}) = -32.8 \text{ kcal-mol}^{-1} \); \( \Delta G(\text{PhMe}) = -34.6 \text{ kcal-mol}^{-1} \).

Considering the reaction in acetic acid first: the computed \( \text{ortho} \)-C-H activation reaction is both thermodynamically favoured \( \Delta G(\text{PhMe}) = 1.2 \text{ kcal-mol}^{-1} \) and kinetically favoured \( \Delta G^\ddagger = 2.4 \text{ kcal-mol}^{-1} \). Importantly, with this small difference in free-energy barrier heights, the \( \text{peri} \)-C-H activation reaction pathway is still kinetically accessible. If the reaction in AcOH is reversible, which the experimental findings suggest, then these computational findings are consistent with the observation that the reaction in acetic acid-\( d_4 \) produces only \( \text{2}_{\text{ortho}} \), yet the \( \text{peri} \)-site undergoes 100% deuteration. We suggest that the abundant source of protons available in acetic acid renders the reaction readily reversible. However, given the large barrier for the reverse of this computed reaction, the mechanism for this equilibration is unknown.

Considering the reaction in toluene next: the computed \( \text{ortho} \)-C-H activation reaction is still thermodynamically favoured \( \Delta G(\text{PhMe}) = 1.4 \text{ kcal-mol}^{-1} \), but now the difference in free-energy barrier heights is very small \( \Delta G^\ddagger = 0.7 \text{ kcal-mol}^{-1} \). If the reaction in toluene is irreversible, the calculated product distribution \( \text{2}_{\text{ortho}}/\text{2}_{\text{peri}} = 72:28 \) at 100 °C is similar to the experimental observation \( \text{2}_{\text{ortho}}/\text{2}_{\text{peri}} = 55:45 \); indeed, the difference in barrier heights that corresponds to these different product distributions (0.55 kcal-mol\(^{-1}\)) is within the error of the computational method.\(^{20} \) We again suggest that the lack of an abundant proton source in toluene renders the reaction effectively irreversible.
This computational investigation highlights several factors that have the potential to influence the selectivity of C-H activation: (i) the effect of the solvent on the relative energies of products, intermediates and transition states; (ii) whether the conditions of the reaction render it reversible or not; and (iii) the reaction pathways involved. In this study, the transition state for C-H cleavage is always lower for the peri-C-H activation, TS(A-B$_{peri}$) vs. TS(1a-B$_{ortho}$). However, since the peri-C-H activation is a two-step reaction that has a higher energy transition state TS(1a-A) prior to C-H cleavage, the one-step ortho-C-H activation is either kinetically favoured (in AcOH), or has an almost identical activation energy (in PhMe).

**Conclusions**

C-H activation of HL$_{Me}$ with Na$_2$PdCl$_4$ in acetic acid at elevated temperature occurs selectively at the ortho-position of the naphthyl ring to give 2$_{ortho}$. The dichloride intermediate 1a has been isolated.
and shown to convert to 2_{ortho} under similar reaction conditions. DFT calculations have shown that in acetic acid ortho-C-H activation is kinetically accessible (∆ΔG = 2.4 kcal mol⁻¹). Indeed, peri-deuteration of 2_{ortho} has been achieved on reaction of HLMe with Na₂[PdCl₄] in acetic acid-d₆. In addition, conversion of 2_{peri} to 2_{ortho} has been shown to occur in acetic acid at high temperature. In contrast, in toluene the reaction is found to be irreversible with the difference in barrier height for ortho- and peri-C-H activation very small (∆ΔG = 0.7 kcal mol⁻¹), a finding that is supported by the observed product distribution for 2_{ortho} and 2_{peri} on heating 1{a} in toluene. Overall, this investigation highlights the potential for a number of factors to influence the selectivity of C-H activation, including the reaction pathway, the solvent, and, for a CMD or AMLA reaction, the ligand functioning as an intramolecular base.

We view these findings are of significant relevance in the pursuit of AMLA reaction, the ligand functioning as an intramolecular base.

Experimental Section

General

All operations, unless otherwise stated, were carried out in vessels open to the air, was added H₂ and the mixture stirred and heated to 100 °C for 24 h resulting in the formation of an orange precipitate. Upon cooling to room temperature, the resulting suspension was filtered to give 2_{ortho} as an orange powder (0.116 g, 85%). Recrystallization from dichloromethane/hexane yielded orange crystals suitable for a single crystal X-ray diffraction study. 1H NMR (CD₂Cl₂) : ∆∆G = 2.4 kcal mol⁻¹). Indeed, a finding that is supported by the observed product distribution for 2_{ortho} and 2_{peri} on heating 1{a} in toluene. Overall, this investigation highlights the potential for a number of factors to influence the selectivity of C-H activation, including the reaction pathway, the solvent, and, for a CMD or AMLA reaction, the ligand functioning as an intramolecular base. We view these findings are of significant relevance in the pursuit of new methods for site-selectivity in catalytic C-H functionalization.

Reaction of HLMe with Na₂[PdCl₄]

To a round-bottom flask, equipped with a stir bar open to the air, was added HLMe (0.100 g, 0.25 mmol), Na₂[PdCl₄] (0.074 g, 0.25 mmol) and glacial acetic acid (5 mL). A condenser was attached and the mixture stirred and heated to 100 °C for 60 h. Upon cooling to room temperature, the resulting suspension was filtered to give 2_{ortho} as an orange powder (0.116 g, 85%). Recrystallization from dichloromethane/hexane yielded orange crystals suitable for a single crystal X-ray diffraction study. 1H NMR (CDCl₃, 500 MHz): δ 1.16 (d, 6H, δHH = 6.9 Hz, CH(CH₃)₂), 1.39 (d, 6H, δHH = 6.9 Hz, CH(CH₃)₂), 2.22 (s, 3H, NCCH₃), 3.07 (sept, 2H, δHH = 6.9 Hz, CH(CH₃)₂), 7.25 (s, 3H, dipp-H), 7.41 (t, 1H, δHH = 7.6 Hz, Ar-H), 7.49-7.54 (m, 2H, Ar-Py-H), 7.60 (d, 1H, δHH = 7.8 Hz, Ar-H), 7.84 (d, 1H, δHH = 7.6 Hz, Ar-H), 8.02 (d, 1H, δHH = 8.0 Hz, Py-H), 8.20 (d, 1H, δHH = 8.0 Hz, Ar-H), 8.35 (d, 1H, δHH = 7.4 Hz, Ar-H), 8.37 (d, 1H, δHH = 8.0 Hz, Py-H). A 13C(C) NMR spectrum could not be obtained due to the sample’s insufficient solubility in CDCI₃ and other common NMR solvents. IR (cm⁻¹): 755 v(C-H bend), 1590 v(C-N) (pyridine), 2666 v(C=O) stretch. ESI MS (+ve, MeOH): m/z 547 [M⁺].

Synthesis of (HLR)PdCl₂ (1a R = Me; 1b R = H)

(a) R = Me (1a). To a 50 mL round-bottom flask, equipped with a stir bar and open to the air, was added HLMe (0.100 g, 0.25 mmol), (MeCN)₃PdCl₂ (0.064 g, 0.25 mmol) and chloroform (5 mL). The mixture was then stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the crude product recrystallized from dichloromethane/hexane to give 1a as an orange powder (0.110 g, 75%). Slow evaporation of a chloroform solution of the product yielded orange crystals suitable for a single crystal X-ray diffraction study. 1H NMR (CDCl₃, 500 MHz): δ 1.19 (d, 3H, δHH = 6.9 Hz, CH(CH₃)₂), 1.23 (d, 3H, δHH = 6.8 Hz, CH(CH₃)₂), 1.42 (d, 3H, δHH = 6.9 Hz, CH(CH₃)₂), 1.46 (d, 3H, δHH = 6.8 Hz, CH(CH₃)₂), 1.58 (s, 3H, NCCCH₃), 2.31 (s, 3H, CH₃), 2.40 (t, 1H, δHH = 7.6 Hz, CH(CH₃)₂), 2.72 (sept, 1H, δHH = 6.8 Hz, CH(CH₃)₂), 2.74 (d, 2H, δHH = 8.0 Hz, dipp-H), 3.13 (t, 1H, δHH = 8.0 Hz, dipp-H), 7.36 (t, 1H, δHH = 6.0 Hz, Ar-H), 7.57-7.65 (m, 3H, Ar- and H bend), 796 ν(C=O) stretch. ESIMS (+ve, MeOH): m/z 547 [M⁺].
To a 50 mL round-bottom flask, open to the air and equipped with a stir bar and open to the air, was added 1a (0.010 g, 0.018 mmol), AgOAc (0.006 g, 0.036 mmol, 2 eq.) and chloroform (3 mL). The mixture was stirred at room temperature overnight, resulting in a white/grey precipitate. Following filtration, the solvent was removed under reduced pressure to give 3peri·AgCl as a yellow powder (0.011 g, 87%).1H NMR (CDCl3, 400 MHz): δ 1.02 (d, 6H, JHH = 6.5 Hz, CH(CH3)2), 1.17 (br s, 3H, Pd-OC(O)CH3), 1.22 (d, 6H, JHH = 6.5 Hz, CH(CH3)2), 2.32 (s, 3H, (CH3)2C=N), 2.96-3.11 (m, 2H, CH(CH3)2), 7.03-7.09 (m, 1H, Ar, Py-H), 7.14-7.16 (m, 2H, Ar, Py-H), 7.19 (s, 2H, Ar, Py-H), 7.50 (t, 1H, JHH = 7.8 Hz, Ar, Py-H), 7.54 (d, 1H, JHH = 7.9 Hz, Ar, Py-H), 7.89 (d, 1H, JHH = 7.6 Hz, Ar, Py-H), 7.95 (d, 1H, JHH = 7.8 Hz, Ar, Py-H), 8.18-8.23 (m, 2H, Ar, Py-H), 8.47 (d, 1H, JHH = 8.4 Hz, Ar, Py-H). HRMS (FAB): calculated for C29H29N2Pd·[M-OAc-AgCl]+: 511.1365, found 511.1357.

(b) Step 2: Intermediate 3peri·AgCl was then dissolved in dichloromethane (5 mL) and stirred vigorously with a saturated aqueous sodium chloride solution at room temperature for 2 h. The organic layer was separated and the aqueous layer washed with dichloromethane (3 × 5 mL). The organic phases were combined, dried over MgSO4 and the solvent removed under reduced pressure affording 2peri as a yellow solid (0.007 g, 73%). The spectroscopic and analytical data were as described above.

Peri-deuteriation of 2ortho
To a 25 mL round-bottom flask, equipped with a stir bar and open to the air, was added HLA (0.005 g, 0.012 mmol), Na2[PdCl4] (0.004 g, 0.012 mmol) and Cd(CO) (3 mL). A condenser was attached and the mixture stirred and heated to 100 °C for 60 h. Upon cooling to room temperature, the resulting suspension was filtered to give the crude product. Recrystallization from CH2Cl2/hexane yielded peri-deuteriated 2ortho as an orange-yellow powder (0.006 g, 87%).1H NMR (CDCl3, 400 MHz): 1.16 (d, 6H, JHH = 6.8 Hz, CH(CH3)2), 1.39 (d, 6H, JHH = 6.8 Hz, CH(CH3)2), 2.22 (s, 3H, NCH3), 3.07 (sept, 2H, JHH = 6.8 Hz, CH(CH3)2), 7.25 (s, 3H, dipp-H), 7.41 (t, 1H, JHH = 7.5 Hz, Ar-H), 7.49-7.54 (m, 2H, Ar, Py-H), 7.60 (d, 1H, JHH = 8.6 Hz, Ar-H), 7.84 (d, 1H, JHH = 8.3 Hz, Ar-H), 8.02 (t, 1H, JHH = 8.3 Hz, Py-H), 8.20 (d, 1H, JHH = 8.3 Hz, Ar-H), 8.35 (d, 1H, JHH = 7.4 Hz, Ar-H).

Thermolysis of 1a in toluene
To a 25 mL round-bottom flask, equipped with a stir bar and open to the air, was added 1a (0.005 g, 0.009 mmol) and toluene (3 mL). Thermolysis of 1a in toluene afforded 2ortho and trace amounts (< 5%) of 2peri.

Conversion of 3peri to 2peri
To a 50 mL round-bottom flask, open to the air and equipped with a magnetic stir bar, was added (Lmx)PdOAc (3peri) (0.051 g, 0.09 mmol), dichloromethane (10 mL) and a saturated aqueous solution of sodium chloride (10 mL). The biphasic mixture was then stirred vigorously overnight to obtain a yellow coloured reaction mixture. The organic phase was then separated and the aqueous layer washed with chloroform (2 × 10 mL). The organic extracts were combined and dried over magnesium sulphate. The solvent was removed under reduced pressure to give 2peri as a yellow-brown solid (0.053 g, 99%). Single crystals could be grown by layering a dichloromethane solution of the complex with hexane. Mp: > 260 °C.1H NMR (CDCl3, 400 MHz): δ 1.06 (d, 6H, JHH = 6.9 Hz, CH(CH3)2), 1.35 (d, 6H, JHH = 6.9 Hz, CH(CH3)2), 2.27 (s, 3H, NCH3), 3.05 (sept, 2H, JHH = 6.9 Hz, CH(CH3)2), 7.16-7.23 (m, 3H, dipp-H), 7.26 (d, 1H, JHH = 7.8 Hz, Ar-H) 7.47 (t, 1H, JHH = 7.8 Hz, Ar-H), 7.58 (d, 1H, JHH = 7.8 Hz, Ar-H), 7.85 (d, 1H, JHH = 7.6 Hz, Ar-H), 7.94 (d, 1H, JHH = 8.0 Hz, Py-H), 8.10 (t, 1H, JHH = 8.0 Hz, Py-H), 8.15 (d, 1H, JHH = 7.4 Hz, Ar-H), 8.40 (d, 1H, JHH = 8.0 Hz, Py-H), 8.61 (d, 1H, JHH = 7.4 Hz, Ar-H).1H NMR (CDCl3, 100 MHz): δ 18.7 (P(C6H5)3), 23.8 (Ar-CH-(CH3)2), 23.9 (Ar-CH-(CH3)2), 28.81 (Ar-CH-(CH3)2), 120.2 (CH), 122.8 (CH), 123.3 (CH), 123.4 (C), 123.9 (CH), 125.5 (CH), 126.4 (CH), 127.0 (CH), 128.3 (CH), 129.3 (CH), 133.8 (C), 134.2 (CH), 134.8 (C), 137.3 (C), 139.0 (CH), 141.0 (C), 142.1 (C), 155.6 (C), 156.3 (C), 171.2 (C-Npyridine). IR (cm⁻¹): 754 v(C=N bend), 795 v(C=N stretch), 1591 v(C-Npyridine), 1627 v(C=Npyridine), 2960 v(C-H stretch). ESI-MS (+ve, MeOH): m/z 547 [M]+. HRMS (FAB): calculated for C29H29N2PdCl [M]+ 547.2023 and C29H29N2Pd·[M]+ 511.1088, found 547.2017 and 511.1079. Mp: > 270 °C. Anal. calc. for (C29H29N2ClPd): C 63.63, H 5.34, N 4.39. Found C 63.57, H 5.46, N 5.39%

Conversion of 1a to 2ortho (3peri·AgCl)
(a) Step 1. To a 25 mL round-bottom flask, equipped with a stir bar and open to the air, was added 1a (0.010 g, 0.018 mmol), AgOAc (0.006 g, 0.036 mmol, 2 eq.) and chloroform (3 mL). The mixture was stirred at room temperature overnight, resulting in a white/grey precipitate. Following filtration, the solvent was removed under reduced pressure to give 3peri·AgCl as a yellow powder (0.011 g, 87%).1H NMR (CDCl3, 400 MHz): δ 1.02 (d, 6H, JHH = 6.5 Hz, CH(CH3)2), 1.17 (br s, 3H, Pd-OC(O)CH3), 1.22 (d, 6H, JHH = 6.5 Hz, CH(CH3)2), 2.32 (s, 3H, (CH3)2C=N), 2.96-3.11 (m, 2H, CH(CH3)2), 7.03-7.09 (m, 1H, Ar, Py-H), 7.14-7.16 (m, 2H, Ar, Py-H), 7.19 (s, 2H, Ar, Py-H), 7.50 (t, 1H, JHH = 7.8 Hz, Ar, Py-H), 7.54 (d, 1H, JHH = 7.9 Hz, Ar, Py-H), 7.89 (d, 1H, JHH = 7.6 Hz, Ar, Py-H), 7.95 (d, 1H, JHH = 7.8 Hz, Ar, Py-H), 8.18-8.23 (m, 2H, Ar, Py-H), 8.47 (d, 1H, JHH = 8.4 Hz, Ar, Py-H). HRMS (FAB): calculated for C29H29N2Pd·[M-OAc-AgCl]+: 511.1365, found 511.1357.

(b) Step 2: Intermediate 3peri·AgCl was then dissolved in dichloromethane (5 mL) and stirred vigorously with a saturated aqueous sodium chloride solution at room temperature for 2 h. The organic layer was separated and the aqueous layer washed with dichloromethane (3 × 5 mL). The organic phases were combined, dried over MgSO4 and the solvent removed under reduced pressure affording 2peri as a yellow solid (0.007 g, 73%). The spectroscopic and analytical data were as described above.

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time period, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. At 24 h, a 83:17 mixture of $F_{\nuclear}$ and $F_{\peri}$ was revealed by $H$ NMR spectroscopy (CDCl$_3$). At 48 h, a 90:10 mixture of $F_{\nuclear}$ and $F_{\peri}$ was shown by $H$ NMR spectroscopy (CDCl$_3$).

Crystalllographic Studies
Data for 1a, 1b, 2$_\nuclear$, and 2$_\peri$, were collected on a Bruker APEX 2000 CCD diffractometer. Details of data collection, refinement and crystal data are listed in Table 4. The data were corrected for Lorentz and polarisation effects and empirical absorption corrections applied. Structure solution by direct methods and structure refinement based on full-matrix least-squares on $F^2$ employed SHELXTL version 6.10. Hydrogen atoms were included in calculated positions (C-H = 0.93 – 1.00 Å) riding on the bonded atom with isotropic displacement parameters set to 1.5 Ueq(C) for methyl H atoms and 1.2 Ueq(C) for all other H atoms. All non-H atoms, were refined with anisotropic displacement parameters. Disordered solvent was omitted using the SQUEEZE option in PLATON for 1b.23

Computational methods
Calculations were performed with Gaussian 09, Revision E.01.24 Geometry optimisations and thermal contributions to energies were computed in the gas phase with the gradient-corrected functional BP8625 and employed the SDD basis set for Pd with the Stuttgart/Dresden 28-electron ECP;26 the 6–31G(d,p) basis set was employed SHELXTL version 6.10.21 Hydrogen atoms were included in calculated positions (C-H = 0.93 – 1.00 Å) riding on the bonded atom with isotropic displacement parameters set to 1.5 Ueq(C) for methyl H atoms and 1.2 Ueq(C) for all other H atoms. All non-H atoms, were refined with anisotropic displacement parameters. Disordered solvent was omitted using the SQUEEZE option in PLATON for 1b.23

Conflicts of interest
There are no conflicts to declare.

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Notes and references
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