Selective *ortho*-C-H activation in arenes without functional groups

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KEYWORDS C-H activation, oxidative addition, iridium, arenes, aromatic substitution

ABSTRACT: Aromatic C-H activation in alkylarenes is a key step for the synthesis of functionalised organic molecules from simple hydrocarbon precursors. Known examples of such C-H activations often yield mixtures of products resulting from activation of least-hindered C-H bonds. Here we report highly selective *ortho*-C-H activation in alkylarenes by simple iridium complexes. We demonstrate that the capacity of the alkyl substituent to override the typical preference of metal-mediated C‑H activation for least hindered aromatic C-H bonds results from transient insertion of iridium into the benzylic C-H bond. This enables fast iridium insertion into the *ortho*-C-H bond, followed by regeneration of the benzylic C-H bond by reductive elimination. Bulkier alkyl substituents increase *ortho*-selectivity. The described chemistry comprises a conceptually new alternative to existing approaches to aromatic C-H bond activation.

Site-selective activation of aromatic C-H bonds is a challenging step important for the synthesis of a range of functionalized aromatic molecules: from pharmaceuticals to polymers.1 An established way to achieve high regioselectivity is to use arenes with heteroatom-containing functionalities able to direct the reagent attack at *ortho*-, *meta*- and even *para*-positions.2 Much more appealing is the activation of non-functionalized alkylarenes, readily available from petrochemical feedstocks; however, such activation remains challenging because alkyl groups have limited directing capacity, which leads to mixtures of products.3 The exceptions are symmetrical dialkylarenes in which functionalization occur at the least sterically hindered position4 and a few monoalkylarenes in which selective activation of *meta-*C-H5and *para*-C-H6 bonds has recently been reported.

Arenes without functional groups are generally modified by electrophilic or transition-metal species, yet the yields of *ortho-*substituted products are less than 67% (Fig. 1). Electrophilic functionalization usually yields mixtures of *ortho*- and *para*-substituted products because the regioselectivity is controlled by electronic factors, resulting in nearly isoenergetic *ortho*- and *para*-arenium-cation-like transition states and less stable *meta-*transition states (Fig. 1A). As a result, the *ortho*/*para* selectivity does not exceed the statistical ratio of 2:1.7 In contrast, metal-mediated C-H activation in alkylarenes typically yields mixtures of the *meta*- and *para*-substituted products, with the typical ratios of 2:14 reflecting the steric accessibility of C-H bonds to the metal center. Few such C-H functionalizations yield more than traces of *ortho*-isomers,4 and in no case does the *ortho-*regioselectivity exceed 58%.8

Here we report an approach for regioselective activation of *ortho*-C-H bonds in alkylarenes using simple iridium complexes (Fig. 1C). The high regioselectivity results from an alkyl substituent acting as an efficient directing group that binds the metal *via* initial benzylic C-H activation, which triggers subsequent oxidative addition of an *ortho*-C-H bond, reformation of the benzylic C-H bond and release of the *ortho*-alkylaryl metal species. The key to enabling this approach was the use of rare iridium complexes, Cp\*Ir(4-alkylarene), which bear a non-planar, “spring-loaded” alkylarene ligand with enhanced reactivity.

We recently demonstrated that Cp\*Ir(4-methylarene) complexes promote selective benzylic C-H activation of the methylarene ligand in the presence of a phosphine ligand.9 Our attempt to extend this reactivity to primary and secondary alkylarenes led to an unexpected switch in selectivity and formation of *ortho*-C-H activation products (Fig. 2). The reaction of isopropylbenzene complex **1a** with PMe3 in *n*‑hexane at 100 °C (Fig. 2A) yielded the product of oxidative addition of an *ortho*-C-H bond, Ir aryl hydride complex **2a** in 99% yield. The use of a larger ligand, PPh3, decreased the yield of the *ortho-*C-H activation product **2a-ph** (67%) and the use of no ligand led to a complex mixture of products. Crystal structures of the C-H activation products **2a-ph** and **2a** as a hydride and bromide species are shown in Figs. 2B and S7.

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Figure 1. C-H activation of alkylarenes. (A) Electrophilic aromatic substitution; (B) Metal-mediated C-H activation; (C) Suggested approach for selective, iridium-mediated *ortho*-C-H activation. a Only *para*-isomers of key intermediates are shown for brevity.



Figure 2. Scope and selectivity of iridium-mediated oxidative addition of *ortho*-C-H bonds in alkylarenes. (A) Selective *ortho*-C-H activation in isopropylbenzene *via* initial 4-arene coordination to Cp\*Ir and thermolysis of the resulting complex 1a in the presence of PMe3 or PPh3; (B) Crystal structure of 2a-ph; (C) *Ortho*-C-H activation of mono- and dialkylarenes by Cp\*Ir complexes; (D) Relative order of *ortho*-C-H selectivity; (E) Scope of *ortho*-C-H activation of alkylarene ligands in complexes 1a-n. Numbers under the arene structures refer to total isolated yields of all C-H activation products. Numbers above the arene structures refer to *ortho-*selectivities determined by integration of the hydride signals in the 1H NMR spectra. a First 8 eq. arene, 1 eq. [Cp\*IrCl2]2, 4 eq. AgBF4, acetone, 24 °C, 16 h; then 2 eq. Cp2Co, benzene, 24 °C, 1 h; b See Ref. 9

We explored how the selectivity of *ortho*-C-H oxidative addition depends on the identity of the alkyl substituent on the arene ring by heating alkylarene iridium complexes **1a‑n** with PMe3 as an added ligand (Fig. 2C). These complexesare accessible from alkylarenes in 75-97% yields *via* a simple two-step procedure (see the Supporting Information). C-H activation of alkylarene ligands in **1a-n** led to high yields of iridium hydrides **2a-n** (87-99%) regardless of the identity of the alkyl substituent (Fig. 2C). The *ortho*-selectivity, however, was the highest with larger alkyl groups (Fig. 2D). As shown in Fig. 2E, arenes with secondary alkyls (*i-*Pr, *s-*Bu, 3-Pent, *c*-Pent, *c*-Hex) underwent *ortho*-C-H activation with ≥91% selectivity (**2a-e)**, while arenes with primary alkyls (Et, *n-*Pr, *n-*Bu, *i*-Bu) gave lower *ortho-*selectivities of 72-79% (**2f**-**2i**). An exception was the bulkiest primary alkylarene in the test - neopentylbenzene, which yielded C-H activation product **2j** with 91% *ortho*-selectivity. An arene with the smallest alkyl substituent, methylbenzene, gave no *ortho*-C-H activation product, but benzyl hydride complex **2k** instead.9 The observed order of *ortho-*regioselectivity *sec-*AlkylAr>*n*-AlkylAr>>MethylAr (Fig. 2D) is opposite to that of the classical electrophilic substitution7a,7b and contrasts with that of known oxidative additions of C-H bonds in alkylarenes which favour *meta*- and *para*‑, but not *ortho-*products.10 The same counterintuitive trend holds for the C-H activation of *para*-substituted dialkylarene ligands (Fig. 2C): for example, in *p*‑isopropylmethylbenzene aromatic C-H activation occurs exclusively next to the isopropyl substituent, but not to methyl (**2m**). Bulkier *p*-diisopropylbenzene gives the product of *ortho*-metallation **2l** exclusively, while smaller *p*-dimethylbenzene yields a 32:68 mixture of *ortho-*and benzyl C-H metallation products **2n**.9

To rationalise the observed counterintuitive regioselectivity, we probed the reaction mechanism by monitoring the model C-H activation in *p*-diisopropylbenzene complex **1l** in the presence of PMe3 in cyclohexane-d12 (Fig. 3A). Complex **1l** was chosen because it exists as a single isomer, which improves the accuracy of kinetic measurements by 1H NMR spectroscopy. The reaction is first-order in **1l** and zeroth-order in the phosphine (Fig. 3A). The initial reaction rates for separate thermolyses of **1l** and its analogue with fully deuterated arene ring, **1l-d4** (Fig. 3B) were within the experimental uncertainty, suggesting that *ortho*-C-H bonds do not participate in the rate-determining step. Contrary to what was expected, the *ortho*-C-D activation in **1l-d4** in *n‑*hexane did not lead to deuterium incorporation in the hydride ligand of **2l-d4**. Instead, deuterium appeared in the methyl groups of the *ortho*-isopropyl group (Fig. 3C). This may result from the intramolecular H/D redistribution between the deuteride ligand and the methyl groups. Intermolecular H/D scrambling between the hydride (deuteride) ligand and the solvent was excluded because heating **1l** in cyclohexane-d12 did not lead to D incorporation into **2l** (Fig. 3A). The observed H/D redistribution in **2l-d4** must have resulted from H/D scrambling in reaction intermediates, not in the starting complex **1l-d4**, in which no H/D redistribution was observed over the course of the reaction.

We identified a mechanism that agrees with the observed experimental observations for the *ortho*-C-H activation in **1l** by computing a range of reaction paths using M06-2X functional (Figs. S8-S11). The lowest energy path (Fig. 4A, Path 1) starts with sliding of the arene ligand to give ‑arene intermediate **3**, which then oxidatively adds the benzylic C-H bond of the adjacent isopropyl group. The resulting -benzyl hydride complex **4** isomerises into metallacycle **5** by iridium insertion into the adjacent *ortho*-C-H bond. A quick elimination of the benzylic C-H bond in **5** forms coordinatively unsaturated aryl hydride **6**, which binds PMe3 to afford the observed product **2l**. The similar energies of the four least-stable transition state of the main mechanism (21.2-23.3 kcal/mol) preclude unambiguous identification of the rate-determining step.11 The lack of primary KIE in **1l-d4** *vs* **1l**, however, suggests that oxidative addition of an aromatic C-H bond in **4** is not the rate-determining step.



Figure 3. Mechanistic experiments using model *ortho-*C-H activation in 1l. (A) The model reaction and rate law measurement upon thermolysis of 1l in cyclohexane-d12 in the presence of PMe3; (B) H/D Kinetic isotope effect measured for separate thermolyses of 1l and 1l-d4 in cyclohexane-d12 at <15% conversion; (C) Н/D scrambling upon thermolysis of 1l-d4 in *n*‑hexane. The values in blue show the D content in the specified positions. aMeasurements were conducted at 75 °C.

This mechanism revealed that the observed selective *ortho*-C-H activation in iridium -arene complexes results from the favourable combination of the kinetic and thermodynamic factors that promote site selective aromatic C-H activation and disfavour competing benzylic C-H activation. The *ortho*-C-H activation is kinetically favoured because of the specific directing effect of an alkyl group (Fig. 4A). The coordinated alkylarene substrate undergoes the initial benzylic C-H activation of the alkyl group that anchors the metal centre next to an *ortho*-position and thus promotes the oxidative addition of the *ortho*-C-H bond followed by the facile formation of the final product via the fleeting iridacyclobutane dihydride intermediate **5**. This strained and bulky metallacycle has high free energy (16.8 kcal/mol above the starting complex **1l**) and high reactivity (5.9 kcal/mol barrier for the conversion to **6**), which precluded the detection of the intermediate. However, more stable analogues of **5** with less bulky ancillary and hydrocarbyl ligands12 and their proposed intermediacy in a related isomerisation of *ortho*-methylaryl to benzyl complexes were reported.13 As can be seen in Fig 4A, the *ortho*-C-H activation via the sequential oxidative addition of two C-H bonds indeed requires traversing much smaller barriers (≤23.3 kcal/mol, Path 1) than the standard direct *ortho*-C-H oxidative addition in **3** (31.3 kcal/mol, Path 2).



Figure 4. Mechanistic insight into C-H activation in 1l. (A) Calculated mechanisms for aromatic and benzylic oxidative addition of *ortho*-C-H and benzylic C-H bonds in 1l. All calculations were done with M06-2X functional using the def2SVP basis set for geometry optimizations and frequency calculations and def2TZVPP for single-point energy calculations. All free energies are relative to 1 mole of 1l and 1 mole of PMe3 at 75 °С in cyclohexane (represented in computations by the conductor-like polarizable continuum model). (B) Proposed mechanism for the observed intramolecular H/D scrambling in 1l-d4.

The *ortho*-C-H activation in **1l** (Fig. 4, Path 1) is thermodynamically preferable than the competing benzylic C-H activation (Fig. 4, Path 3) that occurs via the same intermediate **4** and gives exergonic benzyl complex **7**. In contrast, С-H activation in the less bulky iridium methylarene complexes selectively yields benzylic products, which are kinetically and thermodynamically more accessible than the corresponding *ortho*-methylaryl products as we reported previously.14 This comparison of the C-H activation in secondary alkylarene and methylarene iridium complexes suggests that the higher degree of substitution at the benzylic carbon destabilises the benzyl *vs* aryl complex and, therefore, promotes aromatic *ortho*-C-H activation at the expense of benzylic C-H activation (Fig. 2C-D).

This reactivity contrasts to the established reactivity of metal complexes towards alkylarenes that favours the activation of *meta*- and *para*-C-H bonds over the activation of benzylic and *ortho*-C-H bonds.10a,10b,15 The reported double C-H activation mechanism overcomes this limitation: the reversible benzylic C-H activation anchors the metal next to *ortho*-positions and lessens the barrier for the following *ortho*-C-H oxidative addition (Fig. 4A).

Finally, the mechanism may explain the remarkable H/D redistribution upon the *ortho*-C-D oxidative addition in **1l‑d4** (Fig. 3C) that yields hydride, not deuteride, product **2l‑d4**.16 Complex **2l-d4** may result from the equilibration of the initial deuteride intermediate **6-iso-d4** with hydride **6‑d4** followed by coordination of PMe3. Although the exact mechanism for this equilibration has yet to be identified, our preliminary calculations suggest it may occur via five-membered metallacycles **8-iso-d4** and **8-d4** and these metallacycles can be accessed from **1l-d4** only *via* **6-iso-d4** (Figs. S8-S15). The equilibrium between **6‑iso-d4** and **6-d4** lies towards hydride **6-d4** because it is favoured entropically, thanks to the 6:1 H:D ratio, and enthalpically, due to the zero-point energy effect, *i.e.*, the preferred location of deuterium in the highest frequency oscillator,17 which is Csp3-D, not metal-D bond. A similar explanation was proposed by Jones *et al.* for the 2.7-fold higher stability of a related deuteride complex Cp\*Rh(PMe3)(C6D4H)D *vs* its hydride isomer Cp\*Rh(PMe3)(C6D5)H in an equilibrium mixture.18

In summary, we presented a conceptually new method for controlling site-selectivity of C-H activation in arenes without directing groups. This method relies on the use of simple iridium (I) complexes that enable highly selective *ortho*-C-H activation in primary and secondary alkylarenes without any functional groups. Key to this selectivity is the transient reversible benzylic C-H activation that brings the metal centre into close proximity to an *ortho*-C-H bond and enables smooth metal insertion into the most sterically hindered position of the aromatic ring. This C-H activation occurs in a highly reactive Cp\*Ir(2-alkylarene) intermediate generated by arene ligand sliding in a Cp\*Ir(4-alkylarene) precursor. Translation of this stoichiometric reactivity into catalytic *ortho-*C-H functionalizations may open new avenues for the selective synthesis of value-added chemicals from unactivated aromatic hydrocarbons. Enabling such synthetic applications will require further improvement of the scope and selectivity of the process, and the design of a catalytic cycle that involves the straightforward formation of the key unsaturated 2-alkylarene iridium intermediate from the free arene and regeneration of this intermediate after C-H functionalization. Work on addressing these challenges is ongoing in our laboratory.

ASSOCIATED CONTENT

Figures S1-S15, Tables S1-S4, experimental procedures for synthetic and mechanistic experiments, NMR and MS spectra for all new compounds, DFT data for all calculated structures (xyz coordinates), XRD data for **2a-ph** and **2a-br** (cif files). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes  
The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the Royal Society of Chemistry (E21-7333927136 to A. G. S.) and Leverhulme Trust (RPG-2018-406 to A. G. S.), EPSRC Early Career Fellowship (EP/L000075/1 to R. B.) and Petroleum Research Fund (58885-ND7 to R. B.) for financial support. Computations were performed in the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1548562. HR-MS analyses were performed by EPSRC UK National Mass Spectrometry Facility at Swansea University.

ABBREVIATIONS

Cp\*, pentamethylcyclopentadienyl; TS, transition state.

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