Benzoate Cyclometalation Enables Oxidative Addition of Haloarenes at a Ru(II) Center

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ABSTRACT: The first Ru(II)-catalyzed arylation of substrates without a directing group was recently developed. Remarkably, this process only worked in the presence of a benzoate additive, found to be crucial for the oxidative addition step at Ru(II). However, the exact mode of action of the benzoate was unknown. Herein, we disclose a mechanistic study that elucidates the key role of the benzoate salt in the C−H arylation of fluoroarenes with aryl halides. Through a combination of rationally designed stoichiometric experiments and DFT studies, we demonstrate that the aryl−Ru(II) species arising from initial C−H activation of the fluoroarene undergoes cyclometalation with the benzoate to generate an anionic Ru(II) intermediate. The enhanced lability of this intermediate, coupled with the electron-rich anionic Ru(II) metal center renders the oxidative addition of the aryl halide accessible. The role of an additional (NMe4)OC(CF3)3 additive in facilitating the overall arylation process is also shown to be linked to a shift in the C−H pre-equilibrium associated with benzoate cyclometalation.

1. INTRODUCTION

The polyfluorobiphenyl unit is a recurrent building block found as a structural component in drugs1a−c and numerous functional materials1d−m such as organic light-emitting diodes (OLEDs)1 and liquid crystals.1n,k,l Although cross-coupling methods can be applied to access these biaryl moieties,2 C−H arylation strategies have been acknowledged as a more sustainable alternative strategy to selectively form aryl−aryl bonds.3 In this context, fluorinated biaryls can be generated under Pd catalysis employing fluoroarenes with coupling partners such as aryl (pseudo-)halides,4a−d aryl boronic donors,4e or simple arenes.4f,g Alternatively, Cu-5 or Au-catalysts6 can be used to promote analogous transformations. Recently, our group expanded upon the range of transition metal catalysts able to promote this particular type of coupling.7 The arylation of fluoroarenes with aryl halides occurred with a Ru(II) catalyst, [Ru(t-BuCN)6][BF4]2, and (NMe4)OPiv, (NMe4)(4-F-C6H4CO2) cocatalysts and (NMe4)OC(CF3)3 as base in t-BuCN (Scheme 1a). Notably, this methodology is the first Ru-catalyzed C−H arylation process operating without the need for a directing group in the arene.

Crucially, this Ru-catalyzed C−H arylation only proceeded when a benzoate salt was present, with all other bases and carboxylates tested unable to switch on the reaction. Indeed, when the arylation of polyfluoroarene 1a was carried out with bromobenzene 2a under optimized reaction conditions in the absence of the benzoate additive, no cross-coupled product 3aa was formed. To further clarify the surprising role of the benzoate source, a stoichiometric arylation between the catalytically active intermediate tetrafluorophenyl−Ru(II) complex Ru1b and 5-bromo-m-xylene 2b was performed

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recently proposed that the mechanism of the Ru(II)-catalyzed reaction to the reactivity of the system. In a similar vein, we have also demonstrated that is highly reactive toward oxidative addition and is essential with the benzoate salt to form an anionic Ru(II) intermediate required for oxidative addition to occur.\(^8\)

Halides involves a bis-cyclometalated Ru(II) species as the key intermediate for oxidative addition with the aryl halide (to form the cationic Ru(II)-species such as Ru1b, which are inert toward oxidative addition with aryl bromides 2, can undergo cyclometalation with the benzoate salt to form an anionic Ru(II) intermediate that is highly reactive toward oxidative addition and is essential to the reactivity of the system. In a similar vein, we have also recently proposed that the mechanism of the Ru(II)-catalyzed C–H arylation of N-chelating substrates with aryl (pseudo)-halides involves a bis-cyclometalated Ru(II) species as the key intermediate required for oxidative addition to occur.\(^8\)

Herein, we report mechanistic studies elucidating the role of the benzoate salt. Our experiments demonstrate that aryl–Ru(II) species such as Ru1b, which are inert toward oxidative addition with aryl bromides 2, can undergo cyclometalation with the benzoate salt to form an anionic Ru(II) intermediate that is highly reactive toward oxidative addition and is essential to the reactivity of the system. In a similar vein, we have also recently proposed that the mechanism of the Ru(II)-catalyzed C–H arylation of N-chelating substrates with aryl (pseudo)-halides involves a bis-cyclometalated Ru(II) species as the key intermediate required for oxidative addition to occur.\(^8\)

**2. RESULTS AND DISCUSSION**

**2.1. Mechanistic Hypothesis for the Role of the Benzoate.** The specific requirement for a benzoate salt for the reaction to proceed led us to hypothesize that the benzoate may be undergoing ortho-C–H activation as its mode of action. Scheme 2 outlines our proposed catalytic cycle for the process. After the initial C–H activation of the fluoroarene 1 to form the cationic fluoroaryl–Ru(II) complex II, a second C–H activation event on the benzoate would generate anionic Ru(II)-species IV featuring a cyclometalated benzoate unit. This more electron-rich Ru(II) intermediate IV would be more reactive toward oxidative addition with the aryl halide (to V) than the cationic complex II or the neutral species III. Reductive elimination from V would then produce the biaryl product. In contrast, an aliphatic carboxylate such as pivalate would be unable to undergo cyclometalation and thus would be unable to promote the desired arylation reaction. Indeed, whereas the cyclometalation of aromatic benzoates by Ru(II) complexes is well-known and recognized the more challenging β-cyclometalation of aliphatic carboxylic acids has yet to be observed.

**2.2. Kinetic and Isotopic Studies.** With this mechanistic framework in mind and given the possibility of isolating cationic intermediate II, we decided to examine stoichiometric arylation reactions to directly probe the cyclometalation and the oxidative addition steps without interference from the initial C–H activation of the fluoroarene (from I to II, Scheme 2). Thus, we started investigating the kinetic profile of the coupling of pentafluorophenyl–Ru(II) species Ru1c with bromoarene 2b in the presence of a variety of benzoate derivatives (Figure 1). In order to standardize the measure-

![Figure 1. Stoichiometric arylation of Ru1c with 2b employing (NMe4)-2,6-disubstituted benzoates or simple benzoate in the presence or in the absence of (NMe4)OC(CF3)3 base. Yield determined by GC-FID using hexadecane as internal standard.](image-url)

ments, Ru1c was preincubated for 20 min at 90 °C with the benzoate salt prior to the addition of 2b. In agreement with our hypothesis, 2,6-disubstituted benzoate sources, which cannot undergo ortho-C–H activation, did not give any biaryl 3cb irrespective of the electronic effect of these groups (Me, F, OMe). Instead, paralleling our previous observations, (NMe4)-(C6H5CO2) triggered the desired coupling. In view of the often reversible nature of the C–H activation in Ru(II) catalysis,\(^11\) we predicted that the addition of an external base would shift the equilibrium III–IV toward IV (Scheme 2), thus enhancing the reactivity. Indeed, when (NMe4)-(C6H5CO2) was used in combination with the base (NMe4)-OC(CF3)3, a conspicuous acceleration of the rate of arylation was obtained.\(^12\) These data strongly suggest that the proposed ortho-metalation to generate intermediate IV is a key step en route to the formation of the aryl–aryl bond.

In order to test this hypothesis further, catalytic arylation of nonvolatile polyfluoroarene 1a with bromoarene 2b was carried out utilizing the deuterated (NMe4)(C6D5CO2) under standard optimized reaction conditions\(^7\) (Scheme 3).
Analysis of the reaction mixture after 15 min revealed the formation of biaryl 3ab in 16% yield. More importantly, recovered fluoroarene 1a showed 14% deuteration, and recovered benzoic acid revealed a 41% H enrichment at the ortho positions. Since the only source of D was the benzoate salt, this experiment highlights the reversible nature of the steps from intermediate I to IV of the catalytic cycle (Scheme 2) and provides further evidence for the cyclometalation of the benzoic acid. Unfortunately, all attempts at isolation or in situ detection of IV starting from Ru1c in the presence of benzoate salts were unsuccessful, and this likely reflects the high energy of intermediate IV (see SI, section 5 for details and DFT studies below).

2.3. Hammett and Jaffe Plots. In order to gain further mechanistic insights into the cyclometalation step of the benzoate additive, we compared the initial rates of formation of biaryl 3cb in the stoichiometric arylation reactions of Ru1c with 2b in the presence of a variety of electronically diverse 4-substituted benzoate salts (Table 1). First, and surprisingly, the rate of arylation (kobs) increased with both electron-rich and electron-poor benzoates, with the parent unsubstituted benzoate displaying the slowest rate. A second observation from these data can be extracted from the corresponding Hammett plots (Figure 3). Since both meta and para positions to the substituent are potentially involved in the process, we plotted log(kX/kH) versus both σm and σp. In both plots most substituents fit well to a V-shaped Hammett plot (blue diamonds), suggesting that there are both meta and para effects. Interestingly, there are four clear outliers (red circles and green triangles). From the σ constants of the groups studied, it can be seen that those highlighted in blue have similar σm and σp values. In contrast, the groups in red and green have significantly different values for their σm and σp constants. For example, the OMe and OEt groups have negative σp values (−0.27, −0.24) but positive σm (0.12, 0.10). These two groups show higher reactivity than would be expected from Figure 3, where only their σm or σp are

Scheme 3. Catalytic Arylation of 1a with Bromoarene 2b Employing (NMe4)C6D5CO2.

Table 1. Hammett Plots: Initial Rates Data of the Arylation of Ru1c with Bromoarene 2b Employing Different 4-Substituted Benzoates.

| Entry | σm | σp | kobs (%/min) | log (kX/kH) |
|-------|----|----|--------------|-------------|
| 1     | -0.16 | -0.83 | 1.7334 | 0.4906 |
| 2     | -0.10 | -0.20 | 0.7858 | 0.1470 |
| 3     | -0.07 | -0.17 | 0.7283 | 0.1140 |
| 4     | 0     | 0     | 0.5602 | 0 |
| 5     | 0.16  | 0.18 | 1.0770 | 0.2839 |
| 6     | 0.26  | 0.27 | 1.8236 | 0.5126 |
| 7     | 0.38  | 0.35 | 2.5290 | 0.6546 |
| 8     | 0.43  | 0.54 | 2.7943 | 0.6979 |
| 9     | 0.12  | -0.27 | 1.7610 | 0.4974 |
| 10    | 0.10  | -0.24 | 1.5220 | 0.4341 |
| 11    | 0.25  | -0.03 | 2.4571 | 0.6411 |
| 12    | 0.34  | 0.06 | 1.7222 | 0.4877 |

Figure 2. Stoichiometric arylation of Ru1c with 2b employing (NMe4)(C6H5CO2) or (NMe4)(C6D5CO2) and (NMe4)OC(CF3)3 base. Initial arylation rates in formation of 3cb were determined by GC-FID using hexadecane as internal standard.
considered in isolation. This implies that opposite electronic effects are synergistically combining to lower the overall $\Delta G^\ddagger$, thus enhancing the arylation rate. These observations indicate that both $\sigma_m$ and $\sigma_p$ must be considered at the same time. This is reasonable in the system under study as both the kinetically relevant cyclometalation (III to IV) and the rate-limiting aryl bromide oxidative addition (IV to V) steps may be affected by electronic perturbation at the meta and para sites of the benzoate substrates (CAr–H ($\sigma_m$), C(O)O–H ($\sigma_p$), CAr–[Ru] ($\sigma_m$), C(O)O–[Ru] ($\sigma_p$)) at several points in the arylation process (Figure 4). We return to deconvolute these meta and para effects in the computational section below.

Importantly, considering the Hammett equation, eq 1, a Hammett plot should only result in a linear free energy relationship (LFER) if the electronic influence of the R group affects only one position of the aromatic (meta or para) for a kinetically relevant step (i.e., if $\rho_p\sigma_p \gg \rho_m\sigma_m$ or $\rho_m\sigma_m \gg \rho_p\sigma_p$).

\[
\log\left(\frac{k_X}{k_H}\right) = \rho_m\sigma_m + \rho_p\sigma_p
\]  

(1)

Although V-shaped Hammett plots are usually associated with a change in the mechanism of the process, the lowering of the overall $\Delta G^\ddagger$ due to a weighed variation of the electronic properties of the meta and para positions of the benzoates associated with the kinetically relevant cyclometalation provides a more logical explanation for our experimental data (see also the DFT studies below). To validate further this hypothesis, we applied Jaffe’s analysis of the Hammett equation to our system. This modification allows the correlation of substituent perturbations that influence more than one reactive center at the same time to be plotted (Figure 5). In the Jaffe equation, the Hammett equation is divided by one of the two $\sigma$ values. Depending on which $\sigma$ constant is in the denominator, the slope of the plot gives one $\rho$ value, while the y-intercept provides the other $\rho$ value (eqs 2 and 3). In order to verify the LFER, both plots should result in the same values of $\rho_m$ and $\rho_p$. As shown in Figure 5, this treatment of the data led to two plots showing a LFER valid for all the substituents. Similar $\rho$ values were obtained in both cases ($\rho_m \cong 2.2$; $\rho_p \cong -1.2$), thus validating our mechanistic framework.
and by meta-EWGs, which is consistent with the observation that OMe and OEt substituents are visibly outliers in both V-shaped Hammett plots. Importantly, as the meta effect is more significant than the para one, it should also be noted that in the para V-shaped Hammett plot both OPf and F significantly deviate from linearity, as both rates are largely underestimated due to the greater contribution of the meta effect. Instead in the meta V-shaped Hammett plot OPf and F are marginally underestimated and overestimated, respectively. Although both substituents have positive $\sigma_m$ (F = 0.34, OPf = 0.25), OPf has a slightly negative $\sigma_m$ (−0.03), while F has a slightly positive one (0.06), which explains why OPf lies above and F below the linear fitting.

Jaffé equation:

$$\log \left( \frac{k_\text{OPf}}{k_\text{F}} \right) = \frac{\rho_\text{OPf} \sigma_\text{OPf}}{\sigma_m} + \rho_m$$

(2)

Jaffé equation:

$$\log \left( \frac{k_\text{OPf}}{k_\text{F}} \right) = \frac{\rho_m \sigma_\text{OPf}}{\sigma_p} + \rho_p$$

(3)

2.4. DFT Studies. We have also probed the mechanism of these benzoate-assisted arylation reactions with density functional theory (DFT) calculations. The reaction of a model system, $\text{[Ru(C}_6\text{F}_5\text{(MeCN)}_3]^+}$ (denoted $\text{II}^+$), with PhBr in the presence of PhCO$_2$H was considered, with all geometries optimized with the BP86 functional using a modest basis set (BS1, see Computational Details, SI, section 9). Energies were then recomputed using the oB97X-D functional with a def2-TZVP basis set and incorporating MeCN solvation via a PCM correction. Test calculations indicated the use of MeCN in place of the $\text{RI}$-$\text{BS2, acetonitrile}$ during further calculations (see below, Figure 9a). Starting with $\text{[Ru(C}_6\text{F}_5\text{(MeCN)}_2]^+}$, $\text{II}^+$, exchange of two MeCN ligands with PhCO$_2$H yields $\text{mer-[Ru(C}_6\text{F}_5\text{(MeCN)}_2(\text{H}_2\text{-PhCO}_2\text{H})]}$, $\text{mer-II}^+$, which at $-5.57$ kcal/mol proves to be the most stable intermediate prior to the C–H and C–Br bond activation events. Further MeCN/PhCO$_2$H substitution forms $\text{[Ru(C}_6\text{F}_5\text{(MeCN)}_2(\text{H}_2\text{-PhCO}_2\text{H})]}$, $\text{Int(III}^+\text{IV})$ at $-4.57$ kcal/mol. This species then undergoes a 2-step C–H activation via agostic intermediate $\text{Int(III}^+\text{IV})$ at $+4.53$ kcal/mol from which C–H bond cleavage proceeds via an AMLA-6/CMD (ambiphilic metal–ligand assistance/concerted metalation deprotonation) transition state, $\text{TS-(III}^+\text{IV})$, at $+15.63$ kcal/mol (see also Figure 7 for geometric details). This gives a cyclometalated species $\text{Int(III}^+\text{IV})$ at $+9.62$ kcal/mol, and the formation of $\text{fac-IV}$ is endergonic by 15.19 kcal/mol. Alternative C–H bond activation mechanisms were also assessed and shown to be energetically less accessible (Figure 7 and Figure S8 and S9). This transition state for external CMD at $\text{[Ru(C}_6\text{F}_5\text{(MeCN)}_2(\text{H}_2\text{-PhCO}_2\text{H})]}$ by PhCO$_2$H lie above 30 kcal/mol. A direct role for $\text{OC(CF}_3\text{)}_3$ as a base in
C–H activation was also ruled out, either as an external CMD process or as an intramolecular base (AMLA-4/CMD). We return to the role of “OC(CF₃)₃” in promoting the arylation reaction below.

PhBr activation at fac-IV requires initial MeCN substitution and, in principle, could occur at 6-coordinate [Ru(C₆F₅)- (MeCN)₃(k−C₆O-C₆H₄CO₂)(PhBr)]⁺, or as a concerted oxidative addition to yield 18e⁻Ru[(IV) (MeCN)₃(k−C₆O-C₆H₄CO₂)(Ph)(Br)]⁺ or via nucleophilic displacement of Br⁻ to form 16e⁻Ru(C₆F₅)(MeCN)₃(k− C₆O-C₆H₄CO₂)(Ph) (see Figure 8 and Figures S10 and S11).

Such processes, however, proved to have very large barriers. Instead a second MeCN ligand is lost to form square-planar 14e⁻Ru(IV) [Ru(C₆F₅)- (MeCN)₂(k−C₆O-C₆H₄CO₂)(Ph)(Br)]⁺ or via nucleophilic displacement of Br⁻ to form 16e⁻Ru(C₆F₅)(MeCN)₃(k− C₆O-C₆H₄CO₂)(Ph) (see Figure 8 and Figures S10 and S11).

Figure 8. Geometries of alternative C−Br activation transition states with selected key distances in Å and relative free energies in kcal/mol (L = MeCN, Ar¹ = C₆F₅). Examples shown are the lowest energy transition states located for each process; full details of isomers are in the SI (Figures S10 and S11). Data in parentheses are those where the PCM correction for acetonitrile solvent is included in the optimization procedure.

The data in Table 2 indicate that the overall barrier to arylation (ΔG⁺(pub)) depends more on the free energy change of the C−H activation (ΔGCHA) rather than the subsequent barrier to PhBr activation (ΔG⁺(PhBr)). The variation in ΔGCHA is mirrored in the trend in the 2-step C−H activation (G → I: R = NMe₂ + 12.23 kcal/mol < R = CF₃ + 13.74 kcal/mol < R = H (14.47 kcal/mol)). The fact that both an electron-donating and an electron-withdrawing substituent reduce the barrier to C−H activation over the unsubstituted parent has parallels in the trends computed by Gorelsky and Fagnou for Pd(Ph)(OAc)₃ in H activation over the unsubstituted parent has parallels in the trends computed by Gorelsky and Fagnou for Pd(Ph)(OAc)₃.

As highlighted in Figure 4, electronic perturbation arising from the benzoate substituent, R, could manifest itself at the CAr bond, which will be more dependent on σ aryl-C(O)O than on the subsequent C−H activation (ΔGCHA) rather than the subsequent barrier to PhBr activation (ΔG⁺(PhBr)). The variation in ΔGCHA is mirrored in the trend in the 2-step C−H activation (G → I: R = NMe₂ + 12.23 kcal/mol < R = CF₃ + 13.74 kcal/mol < R = H (14.47 kcal/mol)). The fact that both an electron-donating and an electron-withdrawing substituent reduce the barrier to C−H activation over the unsubstituted parent has parallels in the trends computed by Gorelsky and Fagnou for Pd(Ph)(OAc)₃ in H activation over the unsubstituted parent has parallels in the trends computed by Gorelsky and Fagnou for Pd(Ph)(OAc)₃.

As highlighted in Figure 4, electronic perturbation arising from the benzoate substituent, R, could manifest itself at several points along the reaction pathway. The initial chloride abstraction involving CAr−H bond cleavage and formation of a CAr−[Ru] bond, both of which should be sensitive to σ aryl similarly this process involves varying the C(O)O−[Ru] interaction and H⁻ transfer to a second benzoate to form a C(O)O−H⁻ bond, which will be more dependent on σ aryl. As discussed above, the C−Br activation step shows little dependence on R, so we have focused on deconvoluting how σ aryl and σ σ aryl affect ΔGCHA.
To this end, we have computed the free energy changes for the model cyclometalation processes (eqs 4 and 5) for all the 4-R-C₆H₄CO₂⁻ substrates studied experimentally (see Figure 10 and Table S5). In eq 4 cyclometalation of the parent benzoate in E proceeds with different 4-R-C₆H₄CO₂⁻ acting as the base: ΔG(4) should therefore reflect how σ_p promotes C−H activation. In eq 5, the cyclometalation of different 4-R-C₆H₄CO₂⁻ in E proceeds with the parent benzoate acting as the base. ΔG(5) should be dominated by the breaking of the C−H bond and the formation of the new [Ru]−C₆ bond and, as such, should correlate with σ_m. However, σ_m may also play a role here by influencing how the C(O)O−[Ru] interaction varies due to the k²−k¹ change in substrate binding mode. This point was considered in process 6 and was found to be favored by electron-donating para-substituents. This effect is relatively weak, however, with a plot of ΔG(6) vs σ_p giving a straight line of gradient 2.1 (R² = 0.92, see Graph S9).

Figure 9. (a) Kinetic model for the reaction of II’ (denoted A in the kinetic model) with PhBr in the presence of benzoates 4-R-C₆H₄CO₂⁻ to give Int(V’−VI’)(denoted N; L = MeCN, ArF = C₆F₅). Ligand addition steps are assumed to proceed at the diffusion-controlled limit and are indicated by TS energies shown in parentheses. (b) Computed reaction profile (kcal/mol) with PhCO₂⁻ highlighting the effect of the −OC(CF₃)₃ additive; see Figures S12 and S13 for equivalent diagrams computed with 4-NMe₂-C₆H₄CO₂⁻ and 4-CF₃-C₆H₄CO₂⁻. (c) Computed kinetic profiles at 363 K comparing arylation (i) in the presence of PhCO₂⁻, with and without the −OC(CF₃)₃ additive, (ii) in the presence of benzoates 4-R-C₆H₄CO₂⁻ (R = H, NMe₂ and CF₃) without −OC(CF₃)₃ and (iii) in the presence of benzoates 4-R-C₆H₄CO₂⁻ (R = H, NMe₂ and CF₃) with added −OC(CF₃)₃.
Figure 5. is approximately twice as large as the former for the 4-R-C₆H₄CO₂H acids (R = NMe₂, 5.03; R = CF₃, 3.66) are computed of the C Ar

Benzoates giving a value of 102 energies shows little variation as a function of R, with most σ relationship based on the di

Model reactions considered to isolate e counter-

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Distortion of the singlet is most favorable when strong σ-donors adopt a mutually trans arrangement, so the most stable isomers of Ru(IV) species M feature the three strongly donating aryl ligands in a mer configuration. One of these, M(ii), has Ph trans to C6F5 and is actually more stable than M itself (see Figure 13); moreover C–C coupling with the benzoate ligand in M(ii) proceeds through a lower transition state, TS_{M(iii)−N(iii)} (+11.76 kcal/mol), than that for Ph–C6F5 coupling via TS_{M−N} (+14.38 kcal/mol). The fact that benzoate–Ph coupling is not observed is due to M(ii) being kinetically inaccessible, either through C–Br activation at L(ii) (via TS_{L(ii)−M(ii)} +27.63 kcal/mol) or through isomerization of M. The lowest energy isomerization pathway involves Br− loss to form the neutral trigonal bipyramidal intermediate IM−M(ii) followed by Br− reassociation to give M(ii); this second step involves transition state TSM_{M−M(ii)}, which at 17.63 kcal/mol is >3 kcal/mol higher than TSM_{M−N} at 14.38 kcal/mol. Benzoate−C6F5 coupling from either M or M(ii) is also significantly less accessible (see Figure S20). More generally, for the systems in Figure 11 that lack a cyclometalated ligand, C–Br activation is computed to be more accessible when the Ph ligand moves trans to C6F5. The presence of the cyclometalated benzoate therefore promotes the formation of a Ru(IV) intermediate where the Ph and C6F5 can be mutually cis, thus facilitating the observed selectivity of the subsequent C–C coupling.

The computed data highlight how a C–H functionalization process can be promoted through use of a base additive such as (NMe4)OC(CF3)3 and how a subtle perturbation of a C–H activation pre-equilibrium step can have a significant effect on the overall reaction efficiency. Group 1 carbonate salts, M2CO3, have often been proposed as proton sinks in direct arylation reactions,29 and the choice of the Group 1 M+ cation can significantly impact the end result when expressed as a reaction yield. The results here highlight how such variations can result from small changes in the efficiency of these processes that could reflect, for example, changes in additive concentration due to varying solubilities in organic reaction media.

3. CONCLUSIONS

A detailed experimental and in silico mechanistic investigation allowed the elucidation of the role of the benzoate salt in promoting aryl halide oxidative addition in the Ru(II)-catalyzed C–H arylation of fluoroarenes. The inability of 2,6-disubstituted benzoate sources to trigger the desired arylation event, along with D/H scrambling and kinetic isotope effect experiments, supported the hypothesis for the requirement of a cyclometalation step of the benzoate salt. Thus, the resulting highly electron-rich anionic Ru(II) intermediate rapidly undergoes oxidative addition with the
aryl halide to furnish the biaryl product via a selective reductive elimination step. The pre-equilibrium associated with the reversible C–H activation leads to a Jaffe relationship reflecting the influence of the benzoate substituents at multiple distinctive sites in this process. Indeed, simple Hammett plots correlating the electronic perturbation at only one reactive site at the time could not provide a linear free energy relationship that accommodated all the substituents studied.

DFT calculations provide support for a mechanism involving reversible C–H activation and formation of an anionic cyclometalated intermediate. The enhanced lability of this species allows access to a reactive 5-coordinate intermediate capable of C–Br bond cleavage. A kinetic model based on the computed mechanism captures the rate enhancement observed with p-substituted benzoates bearing both electron-withdrawing and electron donating substituents. The role of a (NMee)3OC(CF3)3 additive in promoting reactivity is pinpointed to the deprotonation of the carboxylic acid formed upon cyclometalation that shifts the pre-equilibrium associated with the aryl halide to furnish the biaryl product via a selective reductive elimination step. The pre-equilibrium associated with the deprotonation of the carboxylic acid formed upon cyclometalation that shifts the pre-equilibrium associated with the deprotonation of the carboxylic acid formed at only one reactive site at the time could not provide a linear free energy relationship that accommodated all the substituents studied.

Experimental procedures and characterization data (PDF)
Computed Cartesian coordinates for all stationary points (XYZ)

REFERENCES

(1) (a) Zahn, A.; Brotschi, C.; Leumann, C. Chem. - Eur. J. 2005, 11, 2125–2129. (b) DiMagno, S. G.; Sun, H. Curr. Top. Med. Chem. 2006, 6, 1473–1482. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Chem. Soc. Rev. 2008, 37, 320–330. (d) Liang, T.; Neumann, C. N.; Ritter, T. Angew. Chem. Int. Ed. 2013, 52, 8214–8264. (e) Selby, T. P.; Bereznak, J. F.; Bishara, J. J.; Ding, A. X.; Gopalasamuthiram, V.; Hanagan, M. A.; Long, J. K.; Taggi, A. E. Fungidal substituted azoles. International Patent WO 2009173651 A8, 2009. (f) Gregory, V.; Taggi, A. E. Fungidal Mixtures. International Patent WO 2011056463 A2, 2011. (g) Babudri, F.; Naso, F.; Ragni, R.; Farinola, G. M. Chem. Commun. 2007, 1003–1022. (h) Tang, M. L.; Reichardt, A. D.; Miyaki, N.; Stoltenberg, R. M.; Bao, Z. J. Am. Chem. Soc. 2008, 130, 6064–6065. (i) Wang, Y.; Watson, M. D. J. Am. Chem. Soc. 2006, 128, 2536–2537. (j) Tsuzuki, T.; Shirasawa, N.; Suzuki, T.; Tokito, S. Adv. Mater. 2003, 15, 1455–1458. (k) Weck, M.; Dunn, A. R.; Matsumoto, K.; Coates, G. W.; Lobkovsky, E. B.; Grubbs, R. H. Angew. Chem., Int. Ed. 1999, 38, 2741–2745. (l) Nitschke, J. R.; Tilley, T. D. J. Am. Chem. Soc. 2001, 123, 10183–10190. (m) Kitamura, T.; Wada, Y.; Yanagida, S. J. Fluorine Chem. 2000, 105, 305–311. (n) Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Tokito, S.; Taga, J. Y. Am. Chem. Soc. 2000, 122, 1832–1833.

(2) (a) DePasquale, R. J.; Tamborski, C. J. Org. Chem. 1969, 34, 1736–1740. (b) Coe, P. L.; Pearl, G. M. J. Org. Chem. 1971, 31, 55–57. (c) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. J. Fluorine Chem. 2002, 117, 115–120. (d) Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. Org. Lett. 2005, 7, 4915–4917. (e) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. Angew. Chem., Int. Ed. 2009, 48, 9350–9354. (f) Shang, R.; Xu, Q.; Jiang, Y.-Y.; Wang, Y.; Liu, L. Org. Lett. 2010, 12, 1000–1003. (g) Kinzel, Z.; Zhang, Y.; Buchwald, S. L. J. Am. Chem. Soc. 2010, 132, 14073–14075.

(3) Representative reviews on C–H activation: (a) Alberico, D.; Scott, M. E.; Lautens, M. Chem. Rev. 2007, 107, 174–238. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. Angew. Chem., Int. Ed. 2009, 48, 9792–9826. (c) Gutekunst, W. R.; Baran, P. S. Chem. Rev. 2011, 110, 1976–1991. (d) Lyons, T. W.; Sanford, M. S. Chem. Rev. 2010, 110, 1147–1169. (e) Boorman, T. C.; Larrosa, I. Chem. Soc. Rev. 2011, 40, 1910–1925. (f) Wencel-Delord, J.; Droege, T.; Liu, F.; Gourier, F. Chem. Soc. Rev. 2011, 40, 4740–4761. (g) Arrociam, P. B.; Bruneau, C.; Dineux, P.H. Chem. Rev. 2012, 112, 5879–5918. (h) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Acc. Chem. Res. 2012, 45, 788–802. (i) Juliá-Hernández, E.; Simonetti, M.; Larrosa, I. Angew. Chem., Int. Ed. 2013, 52, 11458–11460. (j) Girard, S. A.; Knauber, T.; Li, C. Angew. Chem., Int. Ed. 2014, 53, 74–100. (k) Kakuki, F.; Kochi, T.; Murai, S. Synlett 2014, 25, 2390–2414. (l) Tani, S.; Uehara, T. N.; Yamaguchi, J.; Itami, K. Chem. Sci. 2014, 5, 123–135. (m) Zhang, X.-S.; Chen, K.; Shi, Z. Chem. Sci. 2014, 5, 2146–2159. (n) Yang, J. Org. Biomol. Chem. 2015, 13, 1930–1941. (o) Dey, A.; Agasti, S.; Maidt, D. Org. Biomol. Chem. 2016, 14, 5440–545. (p) Dey, A.; Maidt, S.; Maidt, D. Chem. Commun. 2016, 52, 12398–12414. (q) Simonetti, M.; Cannas, D. M.; Larrosa, I. In Advances in Organometallic Chemistry; Perez, P. J., Ed.; Elsevier: Amsterdam, 2017, Vol. 67, pp 299–399.

(4) (a) Lafrange, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. J. Am. Chem. Soc. 2006, 128, 8754–8756. (b) Lafrange, M.; Show, D.; Fagnou, K. Org. Lett. 2006, 8, 5097–5100. (c) René, O.; Fagnou, K. Org. Lett. 2010, 12, 2116–2119. (d) Gorelsky, S. I. Coord. Chem. Rev. 2013, 257, 153–164. (e) Wei, Y.; Han, J.; Wang, M.; Su, W.; Hong, M. Org. Lett. 2009, 11, 3346–3349. (f) Wei, Y.; Su, W. J. Am. Chem. Soc. 2010, 132, 16377–16379. (g) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z. Org. Lett. 2011, 13, 276–279.
(a) Do, H.-Q.; Daugulis, O. J. Am. Chem. Soc. 2008, 130, 1128–1129. (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. J. Am. Chem. Soc. 2008, 130, 15185–15192. (c) Do, H.-Q.; Daugulis, O. Chem. Commun. 2009, 6433–6435. (d) Do, H.-Q.; Daugulis, O. J. Am. Chem. Soc. 2009, 131, 17052–17053. (e) Do, H.-Q.; Daugulis, O. J. Am. Chem. Soc. 2011, 133, 13577–13586.

(6) (a) Lu, P.; Boorman, T. C.; Slawin, A. M. Z.; Larrosa, I. J. Am. Chem. Soc. 2010, 132, 5580–5581. (b) Ahlsten, N.; Perry, G. J. P.; Cambero, X. C.; Boorman, T. C.; Larrosa, I. Catal. Sci. Technol. 2013, 3, 2892–2897. (c) Cambero, X. C.; Boorman, T. C.; Lu, P.; Larrosa, I. Angew. Chem., Int. Ed. 2013, 52, 1781–1784. (d) Cambero, X. C.; Ahlsten, N.; Larrosa, I. J. Am. Chem. Soc. 2015, 137, 15636–15639.

(7) Simonetti, M.; Perry, G. J. P.; Cambero, X. C.; Julián-Hernández, F. J.; Arokianathan, J. N.; Larrosa, I. J. Am. Chem. Soc. 2016, 138, 3596–3606.

(8) Simonetti, M.; Cannas, D. M.; Just-Baringo, X.; Vitorica-Yrezabal, I. J.; Larrosa, I. Nat. Chem. 2018, 10, 724–731.

(9) (a) Ackermann, L. Acc. Chem. Res. 2014, 47, 281–295. (b) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. Adv. Synth. Catal. 2014, 356, 1461–1479. (c) Simonetti, M.; Larrosa, I. Nat. Chem. 2016, 8, 1086–1088.

(10) (a) Simonetti, M.; Cannas, D. M.; Panigrahi, A.; Kujawa, S.; Kryjeowski, M.; Xie, P.; Larrosa, I. Chem. Eur. J. 2017, 23, 549–553. (b) Huang, L.; Weix, D. J. Org. Lett. 2016, 18, 5432–5435.

(11) (a) Biafora, A.; Krause, T.; Hackenberg, D.; Belitz, F.; Goofen, L. J. Angew. Chem., Int. Ed. 2016, 55, 14752–14755. (d) Mei, R.; Zhu, C.; Ackermann, L. Chem. Commun. 2016, 52, 13171–13174.

(12) (a) Ackermann, L. Acc. Chem. Res. 2014, 47, 281–295. (b) Ackermann, L.; Vicente, R.; Althammer, A. Org. Lett. 2010, 10, 2299–2302. (c) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. Angew. Chem. Int. Ed. 2011, 50, 5032–5035. Ackermann, L. Chem. Rev. 2011, 111, 1315–1345. (e) Ferrer Flequeu, E.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. J. Am. Chem. Soc. 2011, 133, 10161–10170.

(13) When (2,6-Me-C6H4CO2)(NMe4), (2,6-F-C6H4CO2)(NMe4), and (2,6-O-Me-C6H4CO2)(NMe4) were tested in the presence of added (NMe3)OC(CF3)3, no cross-coupled product was detected.

(14) In light of the reversibility of steps I–IV (Scheme 3), the observed KIE of 1.36 could also be associated with the C–Br activation step of C6F5H/D, which may be generated in situ. In order to rule this hypothesis out, we preincubated C6F5H (1 equiv), [Ru(C6F5)(MeCN)(NMe2, and CF3, respectively, and thus follows the same trend as the data in the table.

(15) (a) Goresky, S. I.; Lapointe, D.; Fagoun, K. J. Am. Chem. Soc. 2008, 130, 10848–10849. (b) Goresky, S. I.; Lapointe, D.; Fagoun, K. J. Org. Chem. 2012, 77, 658–668.

(16) For a recent example where the net effect of arene para substituents is the result of two counter-balancing effects, see: Frasco, D. A.; Mukherjee, S.; Sommer, R. G.; Perry, C. M.; Lambic, N. K.; Abboud, K. A.; Jakubikova, E.; Ison, E. A. Organometallics 2016, 35, 2435–2445.

(17) (a) Eisenstein, O.; Milani, J.; Perutz, R. N. Chem. Rev. 2017, 117, 8710–8753. (b) Clet, O.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; McGrady, J. E.; Perutz, R. N. Acc. Chem. Res. 2011, 44, 333–348.

(18) (a) Evans, M. E.; Li, T.; Vetter, A. J.; Bieth, R. D.; Jones, W. J. Org. Chem. 2009, 74, 6907–6914. (b) Jones, W. D. Inorg. Chem. 2005, 44, 4475–4484.

(19) The higher energy of the Ph–Br activation transition state at [Ru(C6F5)(MeCN)(k^2-PhCO2)](PhBr)− compared to [Ru(C6F5)(k^2-PhCO2)(k^2-PhCO2)](PhBr)− and [Ru(C6F5)(MeCN)(k^2-CO-C6H4CO2)](PhBr)− may reflect the geometry imposed on the metal center by the k^2-PhCO2− ligand (O–Ru–O = 62°) and cyclometalated (C–Ru–O = 82°) ligands; in comparison the O–Ru–O angle in [Ru(C6F5)(MeCN)(k^2-PhCO2)](PhBr)− is 90°. A similar bite angle effect is known to promote oxidative addition in d10 ML2 species by destabilizing an occupied metal-based dπ orbital. The low symmetry of the current systems causes significant orbital mixing and thus complicates a detailed analysis; however, the average energies of the three occupied dπ orbitals in [Ru(C6F5)(k^2-PhCO2)](PhBr)− and [Ru(C6F5)(MeCN)(k^2-CO-C6H4CO2)](PhBr)− are 6–7 kcal/mol above those for [Ru(C6F5)(MeCN)(k^2-PhCO2)](PhBr)−, suggesting that a bite angle effect could also contribute to reducing the barrier to Ph–Br activation here.

(20) Albright, T. A.; Burdett, J. K.; Whango, M. H. Orbital Interactions in Chemistry, 2nd ed.; Wiley, New York, 2013. (c) Wolters, L. P.; Bickelhaupt, F. M. In Computational Studies in Organometallic
The triplet state of the Ru(II) precursors is always strongly disfavored, so C–Br activation pathways computed on the triplet surface were found to be prohibitively high in energy.

(29) (a) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. J. Am. Chem. Soc. 2010, 132, 10692–10705. (b) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. J. Org. Chem. 2010, 75, 8180–8189. (c) Zhang, M.; Huang, G. Chem. - Eur. J. 2016, 22, 9356–9365. (d) Sanhueza, I. A.; Wagner, A. M.; Sanford, M. S.; Schoenebeck, F. Chem. Sci. 2013, 4, 2767–2775.