Computational and synthetic studies on the cyclometallation reaction of dimethylbenzylamine with $[\text{IrCl}_2\text{Cp}^*]_2$: role of the chelating base

BOUTADLA, Youcef, et al.

Abstract

The results of a joint computational and experimental study of the cyclometallation reactions of dimethylbenzylamine (DMBA-H) with $[\text{IrCl}_2\text{Cp}^*]_2$ and a range of chelating bases are presented. With acetate, density functional theory calculations on the key intermediate, $[\text{Ir}(\text{DMBA-H})(\kappa^2-\kappa^1\text{OAc})\text{Cp}]^+$, define a two-step C–H activation process involving initial $\kappa^2-\kappa^1$ displacement of base to give an intermediate that is stabilized by internal H-bonding. Facile C–H bond cleavage then occurs via 'ambiphilic metal ligand activation' (AMLA). A similar pattern is computed for other carboxylates and bicarbonate, and in each case the ease of C–H activation is governed by the accessibility of the $\kappa^2-\kappa^1$ base displacement step; thus, more weakly coordinating bases promote C–H activation. For triflate, $[\text{Ir}(\text{DMBA-H})(\kappa^1-\text{CF}_3\text{SO}_3)\text{Cp}]^+$ is more stable than its $\kappa^2$-isomer and C–H activation proceeds with a barrier of only 3.8 kcal mol$^{-1}$. Experimental studies confirm that a range of carboxylates and triflate can effect cyclometallation; however, reactivity patterns are not consistent with the computed C–H activation barriers. […]

Reference


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Computational and synthetic studies on the cyclometallation reaction of dimethylbenzylamine with [IrCl₂Cp*]₂: role of the chelating base†

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The results of a joint computational and experimental study of the cyclometallation reactions of dimethylbenzylamine (DMBA-H) with [IrCl₂Cp*], and a range of chelating bases are presented. With acetate, density functional theory calculations on the key intermediate, [Ir(DMBA-H)(κ²-OAc)Cp]*, define a two-step C–H activation process involving initial κ–κ` displacement of base to give an intermediate that is stabilized by internal H-bonding. Facile C–H bond cleavage then occurs via ‘ambiphilic metal ligand activation’ (AMLA). A similar pattern is computed for other carboxylates and triflate, and in each case the ease of C–H activation is governed by the accessibility of the κ–κ` base displacement step; thus, more weakly coordinating bases promote C–H activation. For triflate, [Ir(DMBA-H)(κ`-CF₃SO₂)Cp]* is more stable than its κ`-isomer and C–H activation proceeds with a barrier of only 3.8 kcal mol⁻¹. Experimental studies confirm that a range of carboxylates and triflate can effect cyclometallation; however, reactivity patterns are not consistent with the computed C–H activation barriers. Instead, the role of base in opening the [IrCl₂Cp*]₂ dimer and subsequent formation of the [Ir(DMBA-H)(base)Cp*]* intermediates appears crucial. Calculations indicate these processes are far more favourable for acetate than for triflate.

Introduction

Cyclometallation reactions are of current interest for the insight they bring to the general topic of C–H activation.¹ Moreover, cyclometallation is now being exploited in catalytic schemes leading to C–H bond functionalisation,² in particular intramolecular arylation processes.³,⁴ Much of the progress in this area has been based on Pd systems and we⁵ have provided a computational analysis using density functional theory (DFT) of the classic cyclometallation reaction of [Pd(OAc)₂] with DMBA-H⁶ (DMBA-H = dimethylbenzylamine). A number of related computational studies have considered C–H activation in the context of Pd-catalysed arylation reactions and have shown that the base plays a key role in this process.⁶,⁷ Exploitation of the nature and amount of the base employed is often crucial.⁶

In 2003, one of us reported the cyclometallation reaction of DMBA-H with [IrCl₂Cp*].⁸,⁹ Subsequently we used DFT calculations to characterise three different pathways for intramolecular C–H activation in the model intermediate [Ir(DMBA-H)(κ²-OAc)Cp]¹⁰. Of these, the most accessible, Pathway I (ΔE¹ = +16.0 kcal mol⁻¹, see Scheme 1), corresponded to a one-step process involving a 6-membered transition state, where dissociation of one acetate arm is coupled to proton transfer from DMBA-H to the now free arm of acetate. This transition state exhibits a C–H···M agostic interaction and an intramolecular C–H···O H-bond and both features were found to be important in facilitating C–H activation.¹¹ Thus the agostic interaction polarises the C–H bond and so enhances the acidity of the hydrogen which is then readily transferred to acetate. Similarly, strong H-bonding creates a more electron rich C–H bond which in turn facilitates an agostic interaction. These two components act synergically to facilitate C–H bond cleavage via an ambiphilic metal ligand activation process (AMLA).¹²

The two higher energy routes for intramolecular C–H activation, Pathways II and III, both involve initial κ–κ` displacement of acetate such that the free arm is remote from the reacting C–H bond. This resulted in the formation of an intermediate species from which C–H activation can either occur via a 4-membered transition state with H-transfer to the Ir-bound oxygen (Pathway II, ΔE² = +22.8 kcal mol⁻¹), or via an oxidative addition process (Pathway III, ΔE³ = +30.7 kcal mol⁻¹).

In this paper, we focus on the role played by the chelating base in promoting intramolecular C–H activation and have studied a series of [Ir(DMBA-H)(κ²-RCO₂)Cp]* carboxylate complexes, where R = Me, Ph, CF₃ and CCl₃, as well as the bicarbonate (R = OH) and triflate analogues. During this work, we characterized new variants of the reaction profiles described above for [Ir(DMBA-H)(κ²-OAc)Cp]*. These feature a slightly

† Electronic supplementary information (ESI) available: Computed structures and energies for all species. See DOI: 10.1039/b905469c
In the present study a new transition state corresponding to the effects of changing the chelating base ligand on the reaction energetics.

Results and discussion

**[Ir(DMBA-H)](\chi^2\text{-OAc})Cp]**

The reaction profile computed for C–H activation in [Ir(DMBA-H)](\chi^2\text{-OAc})Cp, **I**, via Pathway I is shown in Fig. 1. The structure of **I** is the same as that computed previously, however in the present study a new transition state corresponding to displacement of the proximal (Ir–O1) acetate arm was located (TS(1–2) **I**). This reflects a different angle of approach of the aryl moiety toward acetate which results in both an increase of the Ir–O1 distance (from 2.17 Å in **I**, to 2.77 Å in TS(1–2) **I**) and rotation about the Ir–O2 bond (X–Ir–O2–C2 = 122.2° in **I**, cf. 82.1° in TS(1–2) **I**, where X = the Cp ring centroid). Proton transfer does not occur at this point, but instead TS(1–2) **I** links to a new intermediate, **2** (E = +8.6 kcal mol⁻¹), where further rotation about Ir–O2 has occurred (X–Ir–O2–C2 = 35.2°). O1 is therefore remote from both Ir and the target C1–H1 bond (Ir···O1 = 3.17 Å; H1···O1 = 3.16 Å) and H1 is in fact much closer to the Ir-bound oxygen (H1···O2 = 2.27 Å). As a result, **2** appears ideally set up for proton transfer to **O2** via a 4-membered transition state, although we will show below that this is a high energy process and that proton transfer to **O1** via a 6-membered transition state is still preferred. The acetate ligand itself exhibits very different C–O bond lengths (C2–O2 = 1.12 Å compared to ca. 1.30 Å in **I**) indicative of enhanced single and double bond character, respectively. The shortest contacts between Ir and the aryl moiety involve the Cipso–C1 bond (Ir···Cipso = 2.70 Å; Ir···C1 = 2.50 Å) and an elongation of the Cipso–C1 distance, from 1.41 Å in **I** to 1.43 Å, suggests a degree of η¹-interaction in **2** (other C–C bonds are in the range 1.40–1.42 Å).

To effect C–H activation in **2**, the free acetate arm must approach the C1–H1 bond by rotation about Ir–O2 and in the resultant transition state (TS(2–3) **I**, E = +9.5 kcal mol⁻¹) the X–Ir–O2–C2 torsion angle increases to 68.4°. The approach of the aryl moiety toward the Ir centre also results in a weak agostic interaction (Ir···H = 2.26 Å; Ir···C1 = 2.46 Å; C1···H1 = 1.12 Å) that in turn promotes a C1–H1···O1 H bonding interaction (H1···O1 = 2.12 Å). TS(2–3) **I** therefore exhibits both characteristic features of ambiphilic metal ligand activation and leads to the C–H activated species, **3** (E = −5.7 kcal mol⁻¹).

Fig. 1 illustrates the two-step nature of C–H activation in **I** and shows that the overall rate determining step for this process in **I** will correspond to the initial displacement of acetate to form **2**. This occurs with a computed activation barrier of only 13.4 kcal mol⁻¹. Remarkably, cleavage of the C–H bond in **2** proceeds with a barrier of less than 1 kcal mol⁻¹, despite the absence of any apparent pre-activation in this species. Thus, breaking of the C–H bond is not the difficult step in these intramolecular C–H activation processes. Instead, it is establishing the correct framework for CH cleavage, i.e., making available an intramolecular base and allowing the substrate to approach the metal centre, which incurs the major activation barrier.

Fig. 1 also gives relative energies with inclusion of the effects of solvent polarity (CH₂Cl₂, PCM method, data in italics) and these indicate a reduction in the barrier via TS(1–2) **I** of 1.5 kcal mol⁻¹. In contrast, the final product **3** is destabilized by 1 kcal mol⁻¹, although C–H activation remains exothermic.

Compared to our previous study, the new Pathway I provides a slightly more accessible route for C–H activation (ΔE⁺ = +13.4 kcal mol⁻¹ cf. +16.0 kcal mol⁻¹) and leads to a more stable initial product (ΔE = −5.7 kcal mol⁻¹ cf. −2.4 kcal mol⁻¹). These changes arise from an alternative orientation of the DMBA-H ligand due to different degrees of rotation about the Ir–N and Cipso–Cipso bonds. A similar stabilization of the highest lying transition state along Pathway II was also found (TS(2’–3’) **I**, E = +19.8 kcal mol⁻¹ cf. 22.8 kcal mol⁻¹, see Fig. 2). Location of an analogous oxidative addition transition state with the new
orientation of the DMBA-H ligand failed, as this placed the C1–H1 bond too close to O2 to avoid converging on TS(2’–3’)$^{28}$Me. Instead a new oxidative addition step was defined where the Ir–H bond develops trans to the acetate moiety via TS(2’–3’)$^{28}$Me ($E = +23.2$ kcal mol$^{-1}$, Fig. 2). This is over 7 kcal mol$^{-1}$ more stable than the previous result (Scheme 1), however, TS(2’–3’)$^{28}$Me remains significantly higher in energy than either TS(2–3)$^{28}$R or TS(2’–3’)$^{28}$Me. Full details of the other stationary points along Pathways II and III are given in the ESL†.

The major new feature in the present study is the location of the k1'-intermediate $^{28}$ $^{28}$Me, which appears to be ideally set up for proton transfer onto the Ir-bound oxygen. Moreover, computed natural atomic charges show that O2 actually carries the larger negative charge: $\text{O2} \sim \text{H1}^{+}$. Moreover, computed proton transfer onto the Ir-bound oxygen. Moreover, computed negative charge: $\text{O2} \sim \text{H1}^{+}$.

Computed C–H activation transition states along Pathway II are given, and non-participating H atoms are omitted for clarity.

**Variation of the chelating base ligand**

C–H activation reaction profiles were computed for [Ir(DMBA-H)(κ2'-RCO2)Cp]$^{28}$ species, $^{28}$R, where $R = \text{CCl}_3, \text{Ph}, \text{CF}_3$ and OH. Computation of Pathways I, II and III showed that Pathway I remains the most accessible route in each case and so only the results for this process will be presented. For each system, the rate-determining step for C–H activation along Pathway I corresponds to the κ2–κ1 displacement of the chelating base via TS(1–2)$^{28}$R. The global picture is therefore similar to that already described for the acetate system, however, for each base subtle variations in behaviour were seen and these will be described in turn below. Key geometrical parameters and energies for TS(1–2)$^{28}$R, 2$^{28}$R and TS(2–3)$^{28}$R are shown in Fig. 3, where only the six atoms directly participating in C–H activation are highlighted. These positions encompass the greatest variation in geometry and so the complete structures, which otherwise closely resemble their acetate analogues, are reserved for the ESL† along with details of the various reactant ($^{28}$R) and product ($^{3}$R) species.

**Fig. 2** Computed C–H activation transition states along Pathway II (4-membered, TS(2’–3’)$^{28}$Me) and Pathway III (oxidative addition, TS(2’–3’)$^{28}$Me). Energies (kcal mol$^{-1}$, cf. $^{3}$Me), and selected distances (Å) are given, and non-participating H atoms are omitted for clarity.

**Fig. 3** Computed geometrical parameters (Å and °) for C–H activation in [Ir(DMBA-H)(κ2'-RCO2)Cp]$^{28}$ systems that with $R = \text{CCl}_3$ adheres most closely to the behaviour seen above with acetate. Thus, displacement of the Ir–O1 bond occurs with a similar movement of the carboxylate moiety and rotation about the Ir–O2 bond certainly indicate this is very facile. Recent studies by Ess and co-workers have also highlighted the greater deformation required of the acetate ligand to reach 4-membered transition states for the intermolecular C–H activation of benzene and methane.

Of the four [Ir(DMBA-H)(κ2'-RCO2)Cp]$^{28}$ systems that with $R = \text{CCl}_3$ adheres most closely to the behaviour seen above with acetate. Thus, displacement of the Ir–O1 bond occurs with a similar movement of the carboxylate moiety and rotation about the Ir–O2 bond (X–Ir–O2–C2 = 89.2° in TS(1–2)$^{28}$CCl3 and 28.3° in 2CCl3). When $R = \text{Ph}$ an unexpected result was obtained as the approach of the aryl moiety toward the Ir centre resulted in the displacement of the distal Ir–O2 bond (Fig. 3b). All attempts to find a transition state corresponding to Ir–O1 bond elongation led instead to the C–H activation transition state TS(2–3)$^{28}$Me. The movement of the benzoate moiety is therefore best quantified by the X–Ir–O1–C2 torsion which decreases from 120.3° to 67.4° in TS(1–2)$^{28}$CCl3 through 67.4° in TS(1–2)$^{28}$Ph to 23.2° in TS(2–3)$^{28}$Ph. For R = Ph and CCl3, the κ1'-OC$_2$R intermediates both closely resemble $^{28}$Me, with H1 being closer to the Ir-bound oxygen (2CCl3: H1–O2 = 2.23 Å; 2Ph: H1–O1 = 2.20 Å). There is still only minimal Ir–C1–H1 agostic bonding at this point and the structures differ primarily in the orientation of the carboxylate moiety. When $R = \text{Ph}$ significant rotation about the Ir–O1 bond is required to access the C–H bond...
cleavage transition state. However, as mentioned above, this is a low energy process and ultimately the structure of TS(2–3)k is essentially the same as TS(2–3), and proton transfer proceeds with a barrier of less than 1 kcal mol⁻¹. TS(2–3)k exhibits a later transition state geometry with a longer C1···H1 distance of 1.27 Å and a shorter O1···H1 distance of 1.46 Å, although the barrier to proton transfer is still minimal (1.3 kcal mol⁻¹).

The remaining two systems also react via rate-limiting k⁻→k⁺ displacement of the chelating base and the structures of TS(1–2)k and TS(1–2)k are very similar to TS(1–2)k (see Fig. 3c). Characteristics of these transition states did lead to intermediate structures analogous to 2k. However, in these cases, inclusion of the zero-point energy correction caused the enthalpies of these intermediates to lie above those of the subsequent proton transfer transition states. Thus the very small barriers for proton transfer seen for R = Me, CCl₃, and Ph in fact disappear altogether for R = CF₃ and OH. We therefore consider that TS(1–2)k and TS(1–2)k lead directly to the C–H activation products and so have only shown these stationary points in Fig. 3c.

The energetics of C–H activation computed for all five [Ir(DMBA-H)(κ²-RCO₂)Cp⁺]⁺ species are summarized in Table 1. Barriers to k⁻→k⁺ displacement are highest for MeCO₂⁻ and PhCO₂⁻ and lowest for CCl₃CO₂⁻ and CF₃CO₂⁻ and this reflects the relative coordinating abilities of the various ligands. An approximate correlation between barrier height and the proton accepting ability of the free base is also seen, where the latter is expressed as the negative of the pKₐ of the conjugate acids (final column, Table 1). The relative energies of the intermediates 2k also reflect the coordinating ability of the chelating base, with k⁻→k⁺ displacement being much easier for CCl₃CO₂⁻ (ΔE₁−ₓ = +1.3 kcal mol⁻¹) than for PhCO₂⁻ (ΔE₁−ₓ = +10.1 kcal mol⁻¹) or CH₃CO₂⁻ (ΔE₁−ₓ = +8.6 kcal mol⁻¹).

As explained above, distinct barriers to C–H bond cleavage were only found when R = Me, Ph or CCl₃, although even here these are minimal (<1.5 kcal mol⁻¹). No correlation with the nature of the chelating base is apparent, despite a variation of over 5 orders of magnitude in the proton accepting ability of the free anions. To investigate this we have compared the properties of the k⁺-base moieties in 2k, 2R and 2k with the free anions (see Fig. 4). In the 2k species, the pendant C–O bond is approximately 0.03 Å shorter than the equivalent bonds in the anions, suggestive of enhanced carbonyl character and decreased basicity. Moreover, computed natural atomic charges show a reduction in negative charge associated with the pendant oxygen, q(O₂), in 2k compared to the free anions, q(O₂). For the free anions q(O₂) follows the trend R = CH₃ > Ph >> CCl₃, consistent with the -pKₐ values and the expected donor capacities of the R groups. The difference

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Computed energetics (kcal mol⁻¹) for C–H activation in [Ir(DMBA-H)(κ²-RCO₂)Cp⁺]⁺ species, relative to the appropriate reactant set to zero in each case. -pKₐ values for the conjugate carboxylic acids are also indicated.</th>
</tr>
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<tbody>
<tr>
<td>RCO₂⁻</td>
<td>TS(1–2)k</td>
</tr>
<tr>
<td>CH₃CO₂⁻</td>
<td>13.4</td>
</tr>
<tr>
<td>PhCO₂⁻</td>
<td>14.6</td>
</tr>
<tr>
<td>HOCO₂⁻</td>
<td>11.4</td>
</tr>
<tr>
<td>CCl₃CO₂⁻</td>
<td>9.5</td>
</tr>
<tr>
<td>CF₃CO₂⁻</td>
<td>9.6</td>
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</table>

Fig. 4 | Computed C–O distances (Å) and natural atomic charges on oxygen for intermediates 2k and for the equivalent free anions (average values are given for the latter).

In computed natural atomic charge on O₁ between the free anions and 2k it is much greater for R = Me (Δq = 0.15) and Ph (Δq = 0.11) than for R = CCl₃ (Δq = 0.07) and as a result the total range of 0.12 computed for q(O₂) in the free anions reduces to only 0.05 for q(O₂) in 2k. The effect of the R group on the basicity of the accepting oxygen atom in 2k is therefore much less significant than in the free anions and this accounts for the similar behaviour computed for what initially appears to be a wide range of chelating bases. We noted above that the weakest base of the three, CCl₃CO₂⁻, produces a later transition state structure for the C–H activation step with a greater C–H···Ir agostic interaction and a higher activation barrier. While this is consistent with the trend in q(O₂) (R = Me >> Ph > CCl₃) the differences in the barrier are rather small (ΔE¹ = 0.9 kcal mol⁻¹ for R = Me or Ph cf. 1.3 kcal mol⁻¹ for R = CCl₃).

In contrast to the barriers for C–H bond cleavage, the energy change associated with this step (ΔE₁–ₓ) does correlate with -pKₐ and is most exothermic for CH₃CO₂⁻ and PhCO₂⁻ (ΔE₁–ₓ = -14.3 kcal mol⁻¹ and -15.8 kcal mol⁻¹, respectively) than for CCl₃CO₂⁻ (ΔE₁–ₓ = -5.6 kcal mol⁻¹). Thus, a more favorable (in a thermodynamic sense) C–H bond cleavage (2 → 3) is associated with a less accessible k⁻→k⁺ displacement (1 → 2), and vice versa. The cancellation of these two effects accounts for the remarkable lack of variation in the overall energetics of C–H activation in 1k to give 3k across the whole range of bases studied (ΔE = -5.1 kcal mol⁻¹ ± 0.8 kcal mol⁻¹).

Overall, C–H activation in these [Ir(DMBA-H)(κ²-RCO₂)Cp⁺]⁺ species is characterised by a low energy barrier corresponding to k⁻→k⁺ displacement of the chelating base and follows the trend R = CF₃ > CCl₃ > OH > CH₃ > Ph. The reaction is slightly exothermic in all cases and shows minimal variation in this regard with respect to the chelating base involved. Including solvent polarity effects via PCM calculations did not affect these trends significantly with all the systems behaving in a similar way to that described for acetate above.

[Ir(DMBA-H)(κ²-CF₃SO₂)Cp⁺], 4

The identification of k⁻→k⁺ displacement of base as the rate-determining step for C–H activation, along with the realization that the proton accepting ligand may not need to be strongly basic, led us to target triflate as a co-ligand in intramolecular C–H activation (Fig. 5). As anticipated with such a weakly coordinating species, the k⁻→k⁺ displacement step is very facile and has the smallest barrier computed so far (ΔE¹ = 7.0 kcal mol⁻¹). Moreover, the intermediate formed, [Ir(DMBA-H)(κ²-CF₃SO₂)Cp⁺], 5, is actually 3.0 kcal mol⁻¹ more stable than κ²-4. The geometry of 5
Ir-bound oxygen (H1◊◊◊dichloromethane.

sodium carboxylate, sodium triflate or sodium bicarbonate in (per iridium) of both dimethylbenzylamine and the relevant temperature reaction of \([\text{IrCl}_2\text{Cp}^*]_2\) with 1.25 equivalents. Cyclometallation reactions were carried out through the room attention to the experimental investigation of this reaction. We therefore turned our overcome by displacement of CF3SO3Hb yC l is still small and the endothermicity of this process should be a promising target for experiment as the barrier to C–H activation would be expected to be the dominant form in solution. As such, the C–H activation step becomes rate-determining with 3.8 kcal mol\(^{-1}\), albeit still small in an absolute sense. As seen with the \(\text{Cl}_3\text{CO}_2\) system a higher barrier corresponds to a later transition state geometry and TS(5–6) features both the longest Cl···H1 distance (1.32 Å) and the shortest O1···H1 distance (1.35 Å) of any of the C–H activation transition states computed so far. Despite this, TS(5–6) is over 6 kcal mol\(^{-1}\) more stable than TS(4–5) and in this sense the triflate system behaves in an analogous fashion to the carboxylate and bicarbonate analogues.

Unlike these analogues, however, in this case the \(\kappa^1\)-isomer, 5, would be expected to be the dominant form in solution. As such, the C–H activation step becomes rate-determining with \(\Delta E^\ddagger = 3.8 \text{ kcal mol}^{-1}\), the smallest value for the overall barrier found so far. PCM solvent corrections (italics, Fig. 5) do increase \(\Delta E^\ddagger\) to 6.9 kcal mol\(^{-1}\); moreover the formation of 6 from 5, exothermic by 1.5 kcal mol\(^{-1}\) in the gas-phase, becomes endothermic by 4.1 kcal mol\(^{-1}\) in solution. Despite this, the triflate system remains a promising target for experiment as the barrier to C–H activation is still small and the endothermicity of this process should be overcome by displacement of CF3SO3H by Cl\(^-\) in the final step of the cyclometallation reaction (see below). We therefore turned our attention to the experimental investigation of this reaction.

Experimental studies.

Cyclometallation reactions were carried out through the room temperature reaction of \([\text{IrCl}_3\text{Cp}^*]\), with 1.25 equivalents (per iridium) of both dimethylbenzylamine and the relevant sodium carboxylate, sodium triflate or sodium bicarbonate in dichloromethane.\(^{16}\) Reactions were run for 17 h and then filtered through celite to remove excess salts, and rotary evaporated to dryness. The solid was redissolved in CDCl\(_3\) and mesitylene was added as an internal NMR standard and the yield of the product, \([\text{Ir(DMBA)}(\text{Cl})\text{Cp}^*]\), was estimated by integration. The highest yield was for acetate (65%) then trifluoroacetate (55%) with trichloroacetate (28%) and benzoate (29%) approximately the same. Sodium triflate gave very little conversion after 17 h, however if left longer a reasonable yield of 50% was produced after 4 d. Sodium bicarbonate gave no product even after several days.

The overall rate of formation of the cyclometallated products does not follow a simple relationship with the activation energies computed above for C–H activation in \([\text{Ir(DMBA-H)}(\kappa^2-\text{CF}_3\text{SO}_3)\text{Cp}^*]_2\) and \([\text{Ir(DMBA-H)}(\kappa^2-\text{CF}_3\text{SO}_3)\text{Cp}^*]\). In particular, the reaction with acetate, which has the second highest computed barrier to C–H activation, is actually most efficient, while that with triflate, predicted to have the lowest barrier, is very slow. This indicates that C–H activation is not the rate determining step of the overall reaction. Additional steps that need to be considered are the initial opening of the \([\text{IrCl}_3\text{Cp}^*]\), dimer and the introduction of DMBA-H and the chelating base to the metal centre. We have previously shown that DMBA-H does not react with the \([\text{IrCl}_3\text{Cp}^*]\), dimer in absence of acetate,\(^*\) moreover for the cyclometallation of 2-substituted pyridines, reaction of the \([\text{IrCl}_3\text{Cp}^*]\), dimer with acetate occurs prior to coordination of the pyridine.\(^{17}\) The base therefore plays a dual role in these reactions, inducing dimer opening and acting as an intramolecular base for C–H activation.

In order to assess these additional steps we computed energies for \([\text{IrCl}_3(\kappa^1\text{-base})\text{Cp}^*]\ and \([\text{IrCl}(\kappa^2\text{-base})\text{Cp}]^+\) for the extreme cases where the base is either CH\(_3\)CO\(^-\) or CF\(_3\)SO\(_3\)\(^-\). These complexes represent the likely initial product of dimer opening and one possible intermediate on the pathway to formation of \(2_{\text{act}}/5\), respectively. Combining these results with those for C–H activation in Fig. 1 and 5, and the computed energy of the experimentally-observed cyclometallation product, \([\text{IrCl}(\text{DMBA})\text{Cp}]^+\), allowed us.

**Fig. 5** Computed reaction profile (kcal mol\(^{-1}\)) for C–H activation in \([\text{Ir(DMBA-H)}(\kappa^2-\text{CF}_3\text{SO}_3)\text{Cp}^*]_2\), 4, with selected geometrical parameters (Å and °).

Energies corrected for solvent effects \((\text{CH}_2\text{Cl}_2, \text{PCM method})\) are given in italics, and non-participating H atoms are omitted for clarity.

- TS(4–5) features both the longest Cl···H1 distance (1.32 Å) and the shortest O1···H1 distance (1.35 Å) of any of the C–H activation transition states computed so far.
- TS(5–6) is over 6 kcal mol\(^{-1}\) more stable than TS(4–5) and in this sense the triflate system behaves in an analogous fashion to the carboxylate and bicarbonate analogues.
- Unlike these analogues, however, in this case the \(\kappa^1\)-isomer, 5, would be expected to be the dominant form in solution. As such, the C–H activation step becomes rate-determining with \(\Delta E^\ddagger = 3.8 \text{ kcal mol}^{-1}\), the smallest value for the overall barrier found so far.
- PCM solvent corrections (italics, Fig. 5) do increase \(\Delta E^\ddagger\) to 6.9 kcal mol\(^{-1}\); moreover the formation of 6 from 5, exothermic by 1.5 kcal mol\(^{-1}\) in the gas-phase, becomes endothermic by 4.1 kcal mol\(^{-1}\) in solution.
- Despite this, the triflate system remains a promising target for experiment as the barrier to C–H activation is still small and the endothermicity of this process should be overcome by displacement of CF3SO3H by Cl\(^-\) in the final step of the cyclometallation reaction (see below). We therefore turned our attention to the experimental investigation of this reaction.

**Experimental studies.**

Cyclometallation reactions were carried out through the room temperature reaction of \([\text{IrCl}_3\text{Cp}^*]\), with 1.25 equivalents (per iridium) of both dimethylbenzylamine and the relevant sodium carboxylate, sodium triflate or sodium bicarbonate in dichloromethane.\(^{16}\) Reactions were run for 17 h and then filtered through celite to remove excess salts, and rotary evaporated to dryness.
to construct reaction profiles for both systems (see Fig. 6). The involvement of free anionic bases and Cl⁻ makes the inclusion of CH₂Cl₂ solvation via the PCM method essential and so only the solvent-corrected data are presented.

Further calculations show that C–H activation is controlled by the ease of base displacement and so higher activation barriers are computed with more strongly coordinating bases (R = Me, Ph). For R = CF₃ and OH, C–H bond cleavage occurs without a barrier upon base displacement. In cases where an [Ir(DBMA-H)(κ²-RCO₂)Cp⁺] intermediate was located (R = Me, Ph, CCl₃), the basicity of the free base is shown to be significantly attenuated by binding to the metal centre. For the analogous triflate system [Ir(DBMA-H)(κ²-CF₃SO₃)Cp⁺], 5, was computed to be more stable than its κ¹-isomer and C–H activation proceeds with a barrier of only 3.8 kcal mol⁻¹. The counter-directing effects of coordination strength and basicity mean that the overall energy associated with C–H activation in these species is remarkably insensitive to the intramolecular base employed.

Parallel synthetic studies confirm the ability of a range of chelating bases, including triflate, to effect cyclometallation. However, no simple correlation between reactivity and the computed C–H activation barriers is seen, suggesting that this process is not rate determining in these systems. Instead PCM calculations suggest that opening the [IrCl₂(Cp⁺)] dimer and the subsequent formation of [Ir(DBMA-H)(base)Cp⁺]²⁻ intermediates control reactivity; these steps are much more favourable for acetate compared to triflate.

Conclusions

Density functional theory calculations have been employed to study the role of chelating base, RCO₂⁻ (R = Me, CCl₃, CF₃, OH, Ph), in the cyclometallation reactions of DBMA-H with [IrCl₂(Cp⁺)]. Calculations on C–H activation in [Ir(DBMA-H)(κ²-MeCO₂)Cp⁺] define a two-step process involving initial κ¹-κ¹ displacement of acetate followed by facile C–H bond cleavage.

Notes and references


Fig. 6 Computed energies (kcal mol⁻¹) for key intermediates in the cyclometallation of DBMA-H by [IrCl₂(Cp⁺) in the presence of MeCO₂⁻ (bottom) or CF₃SO₃⁻ (top). All energies include a correction for solvation effects (CH₂Cl₂, PCM method). See Fig. 1 and 5 for full details of the C–H activation steps.

Fig. 6 shows that initial dimer opening is significantly more favourable for acetate (ΔE = −27.1 kcal mol⁻¹) than for triflate (ΔE = −9.1 kcal mol⁻¹). For the acetate system, formation of 2a is then slightly uphill (E = −24.3 kcal mol⁻¹) but is followed by exothermic C–H activation and displacement of HOAc by Cl⁻ that make the overall process very favourable (ΔE = −34.0 kcal mol⁻¹). In contrast, with triflate the formation of 5 and C–H activation are uphill events such that 6 lies 11.8 kcal mol⁻¹ above the reactants. The final displacement of CF₃SO₃H by Cl⁻ is thermodynamically favourable, but the overall reaction remains approximately thermo-neutral (ΔE = −0.2 kcal mol⁻¹). The approximations inherent in the PCM approach mean the absolute energies in Fig. 6 should be treated with caution, especially for small anions where specific solvation will be particularly important. However, the computed trends should be more secure and on this basis the results are consistent with the much more efficient reaction seen experimentally with acetate rather than with triflate. Analogous calculations on the remaining carboxylates and bicarbonate showed behaviour intermediate to that computed with acetate and triflate (see ESI). The failure to observe cyclometallation with bicarbonate therefore appears anomalous. However, a further complicating factor is that these reactions are heterogeneous, in that not all the sodium salts dissolve in dichloromethane. Indeed, the reaction with bicarbonate is the only case in which unreacted [IrCl₂(Cp⁺)] is the sole (Cp⁺Ir) species observed by ¹H NMR spectroscopy.
In this paper, the term ‘cyclometallation’ will be used for the overall reaction starting from [IrCl₂Cp*]₂ and DMBA-H to form the mixture was filtered through Celite and evaporated to dryness. The sample was dissolved in 0.5 mL of a CDCl₃ solution containing mesitylene (0.05 mmol L⁻¹) and the amount of product was determined by integration of the ¹H NMR spectrum. The yield was 65%.

16 In a typical run, a mixture of [IrCl₂Cp*]₂ (20 mg, 0.025 mmol), DMBA-H (8.5 mg, 0.063 mmol) and NaOAc (5.2 mg, 0.063 mmol) in dichloromethane (10 mL) was stirred for 18 h. After this time, the mixture was filtered through Celite and evaporated to dryness. The sample was dissolved in 0.5 mL of a CDCl₃ solution containing mesitylene (0.05 mmol L⁻¹) and the amount of product was determined by integration of the ¹H NMR spectrum. The yield was 65%.
18 In the case of triflate, the ¹H NMR spectrum after 17 h reaction shows almost complete consumption of [IrCl₂Cp*]₂. The calculations are consistent with this, in that while dimer opening appears feasible, the subsequent reaction to the cyclometallated product is then unfavourable.