Article

Mechanisms of C–H bond activation: rich synergy between computation and experiment

BOUTADLA, Youcef, *et al*.

Abstract

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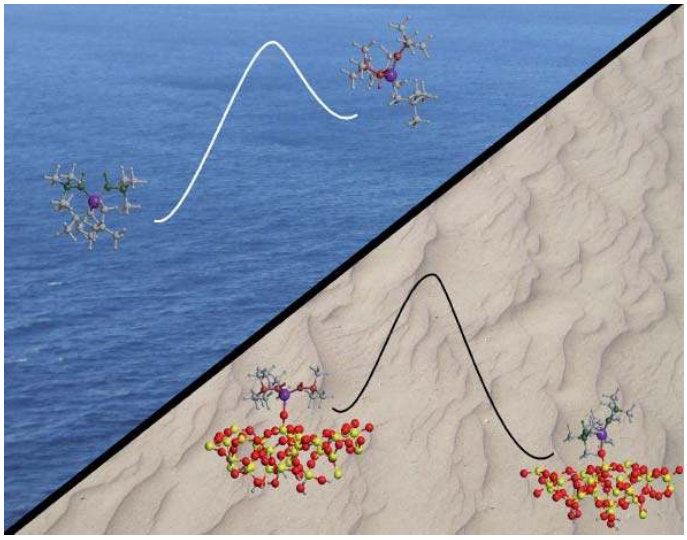

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Mechanisms of C–H bond activation: rich synergy between computation and experiment

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Recent computational studies of C–H bond activation at late transition metal systems are discussed and processes where lone pair assistance *via* heteroatom co-ligands or carboxylates are highlighted as a particularly promising means of cleaving C–H bonds. The term 'ambiphilic metal ligand activation' (AMLA) is introduced to describe such reactions.

1. Introduction

The activation and functionalisation of C–H bonds is one of the most active fields of current chemical research.[1,2] This work is motivated by the desire to make more efficient and effective use of cheap and abundant simple hydrocarbons as feedstocks for chemical synthesis. Central to this goal is the activation of the C–H bond itself. Such bonds can certainly no longer be considered 'inert' and a number of successful catalytic schemes based on intramolecular C–H bond activation have now been realised.[3] Successful catalysis based on intermolecular functionalisation of C–H bonds has also been demonstrated but progress in this area remains a considerable challenge.[4,5a] A thorough understanding of the means by which cleavage of a C–H bond can be achieved remains a key consideration and computational modelling is set to play a central role in providing insight into this process.

From the 1980s, experimental observations of intermolecular C–H activation have been quickly followed by seminal insights from computation and the state of play was summarised in some key reviews in 2000.[6] Over this period, improvements in methodology, in particular the advent of density functional theory (DFT),[7] coupled with improvements in computer power, have resulted in a dramatic expansion in both the range of systems that can be studied and the nature of the problems that can be addressed computationally. Above all, the ability of DFT to routinely define the structures and energies of reactive intermediates and transition states has been particularly important. Such information is, in most cases, very difficult to obtain from experiment. Increasingly, therefore, computational studies are being performed in parallel with experiment, bringing to bear a powerful synergy of complementary techniques to the intricate problem of understanding reaction mechanisms.

In the mid-1990s, mechanisms of C–H activation by organometallic complexes were generally considered to fall into one of three general categories: (i) oxidative addition (OA) at electron-rich low-valent transition metal centres (ii) σ-bond metathesis (SBM) at electrophilic early transition metal (and lanthanide) centres and (iii) electrophilic activation (EA) at electron-deficient late transition metal centres. More recently, the ability to categorise a C–H activation mechanism on the basis of the anticipated behaviour of a given metal centre has become increasingly problematic. One illustrative mechanistic quandary arose with the low-temperature activation of alkanes at $[Cp^*Ir(PMe_3)(CH_3)(OTf)]$.[8] As a late transition metal OA might

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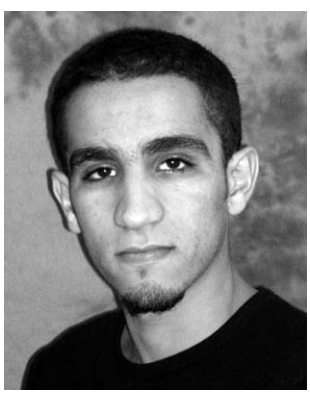
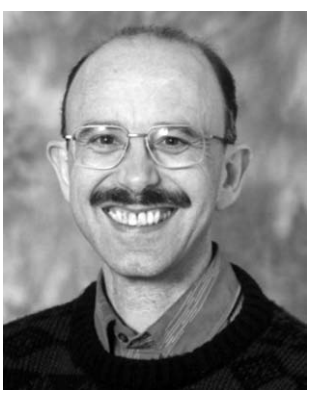


Youcef Boutadla

Youcef Boutadla was born in Paris, France. He completed his undergraduate and Masters in Chemistry at the Université Pierre et Marie Curie in Paris. He started his PhD in the group of David Davies at the University of Leicester in 2006. His research involves mechanistic studies of acetate assisted C–H activation.



David L. Davies

David Davies did his BSc and PhD at Bristol University working with Prof. S. A. R. Knox and was then a NATO postdoctoral fellow at Caltech with Prof. J. E. Bercaw. He was appointed a lectureship at the University of Leicester in 1985, was promoted to senior lecturer in 1999 and to Reader in 2007. His research interests are quite broad encompassing organometallic chemistry and catalysis, with an emphasis on understanding mechanisms.

be anticipated at Ir, but in this case it must be coupled to rapid reductive elimination (RE) as no intermediate was observed. Given the electron-deficient nature of these cationic Ir^{III} species SBM was also considered a possibility (Fig. 1). Calculations ultimately defined an OA/RE pathway in these systems[9,10] and experimental support for this was subsequently gained from the direct observation of Ir^{III}/Ir^{V} C–H bond activation cycles.[11] At the same time, however, calculations on analogous Rh species were consistent with a one step process where the transition state takes on oxidative character normally associated with an OA intermediate (centre, Fig. 1).[12] Further examples of these one-step 'oxidative' reaction steps followed[13] and now it is apparent that SBM is possible at both early and late TM centres. In the following, we shall use the term SBM as a general label for these processes, although, as discussed below, several terms have been proposed by different groups. A further particularly promising development involves the design of well-defined systems with heteroatom-based groups to act as intramolecular H-acceptors. The widening array of systems capable of C–H activation have sparked debate on the mechanisms of this process, an issue computational chemistry is ideally placed to address.

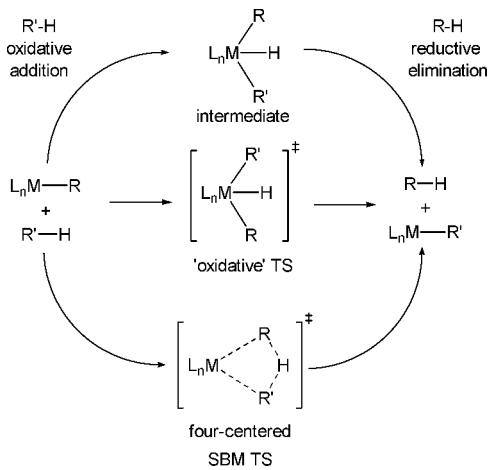


Fig. 1 General mechanisms of C–H activation at L_nM–R species. Adapted from ref. 14.

This perspective will discuss recent mechanistic insights into C–H bond activation arising from computational studies. We will only consider activations involving even electron processes where the metal is directly involved and thus exclude other types of C–H activation such as P450-based or radical processes.[15] Three broad systems, involving middle-late transition metals with d^n ($n \geq 4$), will be considered: (i) SBM processes at L_nM–R Bonds (R = C or B) (ii) systems where a heteroatom-based group bearing lone pairs acts as the H-acceptor (formal 1,2-addition) and (iii) "electrophilic activation" of C–H bonds which involve carboxylate or carbonate as base. In general no mention of the specific methodologies will be given; unless otherwise stated results are based on DFT and the original papers should be consulted for full details.

2. SBM reactions at L_nM–R bonds (R = C or B)

2.1. SBM at L_nM–R bonds (R = alkyl or aryl)

General aspects of this topic have been reviewed recently by Lin[14] who has emphasized the role of occupied metal d-orbitals in stabilizing the transferring hydrogen. As a result, computed transition states often feature short M···H contacts that are consistent with the presence of a M–H bond and Lin has called these 'oxidatively-added transition states' (OATS). The nature of the metal centre can therefore dramatically affect the C–H activation. In their study of $C(sp^3)$-H bond activation at $\{TpM(PH_3)(CH_3)\}$ fragments (M = Fe, Ru, Os; Tp = tris(pyrazolyl)borate) Lin, Lau and Eisenstein showed computed activation barriers increase in the order Os < Ru < Fe (see Fig. 2).[16] Even more striking was the changing nature of the C–H activation process. With M = Os 'normal' 3-centred oxidative addition was characterised, but with the Ru and Fe analogues 4-centred transition states were seen. For M = Ru a very shallow Ru^{IV}–H intermediate was located, while for M = Fe C–H activation was clearly a one-step process *via* a transition state featuring a short Fe···H distance of only 1.53 Å.

A lot of detailed computational work has been carried out on C–H activation at d^6 $\{Ir(acac')_2(R)\}$ and $\{TpRu(L)(R)\}$

Stuart A. Macgregor

Stuart Macgregor received a PhD from Edinburgh University in 1992. After a NATO Western European Fellowship at the Université de Paris-Sud working with Odile Eisenstein and two years at the Australian National University, Canberra, he returned to Scotland in 1997 to take up a lectureship in Inorganic Chemistry at Heriot-Watt University. He was promoted to Reader in 2005 and to Professor in 2008. His research interests lie in the use of computational chemistry to understand the structure and reactivity of transition metal systems, particularly in organometallic chemistry.

Amalia I. Poblador-Bahamonde

Amalia Poblador-Bahamonde was born in Madrid, Spain. After gaining her BSc from the University San Pablo CEU and her MPhil from the University Complutense of Madrid, she started her PhD in the group of Stuart A. Macgregor at Heriot-Watt University, Edinburgh. Her research involves computational studies of C–H activation by half-sandwich complexes.

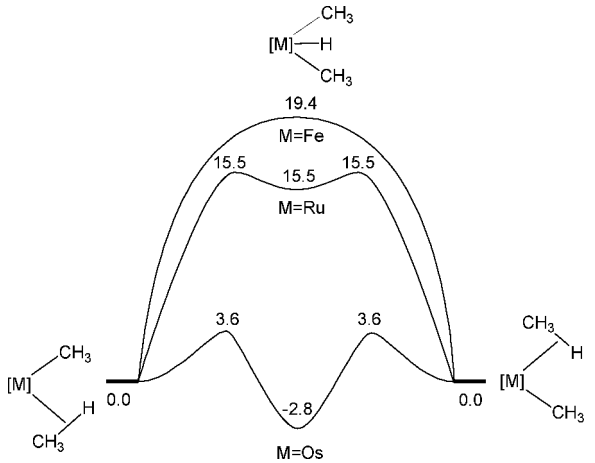
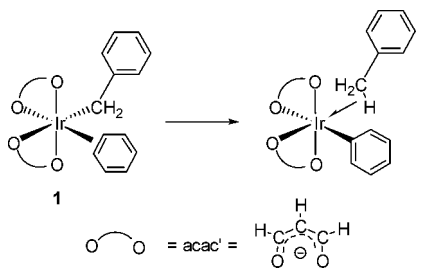


Fig. 2 Computed C–H activation energy profiles (kcal mol^{-1}) for {[M](CH$_3$)(CH$_4$)} species ([M] = TpM(PH$_3$), M = Fe, Ru, Os). Adapted from ref. 16.

fragments, inspired by the role these species play in catalytic alkene hydroarylation (see below). Typical is *cis*-[Ir(acac′)$_2$(CH$_2$CH$_2$Ph)(C$_6$H$_6$)], **1**, in which C–H activation occurs *via* SBM ($\Delta G^{\ddagger}$ = 14.1 kcal mol^{-1}) with an Ir···H distance of only 1.58 Å in the transition state (see Scheme 1). This implies an oxidation of the metal centre, prompting Goddard and Periana to adopt the term 'oxidative hydrogen migration' (OHM) for this type of process.[17] Interestingly, Periana had previously speculated that C–H activation in **1** might proceed *via* an OA pathway,[18] by analogy to Bergman's [Cp*Ir(PMe$_3$)(CH$_3$)(OTf)] system (see Introduction). The fact that a SBM pathway is computed for **1** may reflect an increase in steric crowding and a more electron deficient metal centre, both factors that mitigate against a 7-coordinate Ir(V) intermediate. Certainly distinguishing between these possibilities would have been difficult without computational input.



Scheme 1

Further studies by Periana and Goddard suggest that barriers to these SBM processes can be modulated by the ligand environment. Thus replacing the acac′ ligands in **1** with tropolonate reduces the activation barrier by 2.3 kcal mol^{-1}, a result thought to be related to the more electron-releasing character of the latter.[19] Similarly, although a lower C–H activation barrier was computed for the Ir^{III} complex **1** compared to [TpRu^{II}(CO)(CH$_2$CH$_2$Ph)(C$_6$H$_6$)][20] this trend was reversed by exchanging the ligand sets (*i.e.* [Ru^{II}(acac′)$_2$(CO)(CH$_2$CH$_2$Ph)(C$_6$H$_6$)]$^-$ has a lower barrier than [TpIr^{III}(CO)(CH$_2$CH$_2$Ph)(C$_6$H$_6$)]$^+$).[21] Predicting relative barriers on the basis of metal oxidation state alone is therefore difficult. Further work on isoelectronic d^6 analogues of these complexes yielded a wide range of C–H activation barriers, the lowest being only 0.7 kcal mol^{-1} for [Os^{II}(acac′)$_2$(CO)(CH$_2$CH$_2$Ph)(C$_6$H$_6$)]$^-$. In this case, (as was seen for the [TpOs(PH$_3$)(CH$_3$)(CH$_4$)] system above), C–H activation actually proceeds by an OA pathway.

A more complicated picture of co-ligand effects emerges from work by Gunnoe and Cundari on [TpRu(L)(R)(C$_6$H$_6$)] species. For R = CH$_3$ a lower computed barrier to C–H activation is found when L = PMe$_3$ ($\Delta G^{\ddagger}$ = 10.9 kcal mol^{-1}) compared to L = CO ($\Delta G^{\ddagger}$ = 14.9 kcal mol^{-1}). This is apparently consistent with the ability of the more electron-releasing PMe$_3$ ligand to stabilize 'oxidative character' in the transition state.[22,23] However, steric effects can dominate in these systems in particular, the combination of ligands present is important. Thus when L = CO computed barriers are relatively insensitive to changes in the accepting group, R (R = Ph: $\Delta G^{\ddagger}$ = 15.5 kcal mol^{-1} R = CH$_2$CH$_2$Ph: $\Delta G^{\ddagger}$ = 13.5 kcal mol^{-1}), but activation barriers increase significantly in the more sterically encumbered PMe$_3$ analogues (R = Ph: $\Delta G^{\ddagger}$ = 17.1 kcal mol^{-1}; R = CH$_2$CH$_2$Ph: $\Delta G^{\ddagger}$ = 20.0 kcal mol^{-1}).[24]

These results are all significant in the context of catalytic alkene hydroarylation, which has been demonstrated by both Periana[18] and Gunnoe[25] (Fig. 3). Currently, however, activities are still too low for practical use and one major difficulty in improving performance is the competitive C–H activation of ethene at the 2-phenylethyl intermediate, **2** (see Fig. 4). This releases ethylbenzene (the desired product) but stops catalysis through the formation of a M-vinyl that subsequently inserts another molecule of ethene to form stable η^3-allyl species (**3** in Fig. 4).[26,27] The much stronger binding of ethene results in increased barriers to

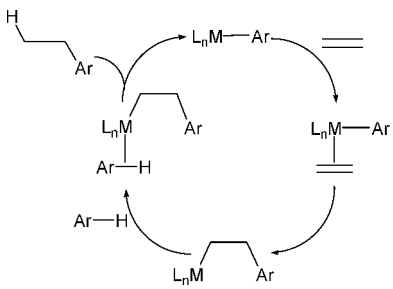


Fig. 3 General catalytic cycle for alkene hydroarylation.

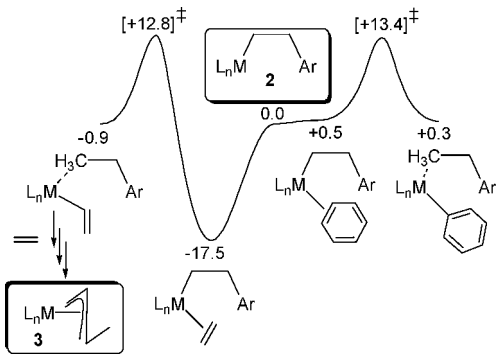


Fig. 4 Calculated free energy profiles (kcal mol^{-1}) for competing C–H activation at intermediate **2** with (right) benzene and (left) ethene. L$_n$M = Ir(acac′)$_2$. Data taken from ref. 17.

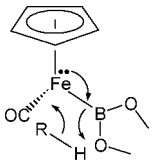
C–H activation. For example C–H activation in *cis*-[Ir(acac′)$_2$-(CH_2CH_2Ph)(C_2H_4)] has a barrier of 30.3 kcal mol^{-1},[17] 17.4 kcal mol^{-1} higher than that for the benzene analogue, but overall the two C–H activation transition states are at very similar energies (Fig. 4). Goddard has highlighted the potentially intrinsic problems in the design of alkene hydroarylation catalysts of this type, in that a more electron rich metal centre that is thought to promote C–H activation would tend to retard the prior alkene insertion step by forming a strongly-bound alkene adduct.[20,21] Ironically, although much attention is focused on the C–H activation it is often the less glamorous components of a catalytic cycle that hamper progress, for example the displacement of ligands to create a vacant site for substrate activation or the 'mundane'[27] alkene insertion step.

Important insight into these SBM processes has been gained by varying the nature of the substrate. Thus, computed barriers for C–H activation in [(Tp)Ru(L)(Me)(*p*-C_6H_5X)] species, yield linear Hammett plots with ρ = 2.6 (L = CO) and 2.3 (L = PMe_3).[23] Electron withdrawing *para*-substituents therefore stabilize the C–H activation transition states, which is opposite to what is expected for classical electrophilic aromatic substitution. These Ru^{II} systems also appear more sensitive to substituent effects than the classic Cp*$_2$Sc-Me system studied by Bercaw.[28] Ru···H distances in these [(Tp)Ru(L)(Me)(*p*-C_6H_5X)] transition states fall in the range 1.592 Å to 1.677 Å with the shortest bond being computed with the most electron withdrawing substituents. Even longer Ru···H distances of *ca.* 1.75 Å had been calculated in earlier studies of C–H activation of the 2-position of THF and thiophene at {(Tab)Ru(CO)Me} (where Tab is the [HB{–N=NH}$_3$]$^-$ model ligand).[29]

In general, more acidic C–H bonds appear easier to activate. Thus activation of a β-C–H bond in Et_2O by {TpRu(PH_3)(H)} showed a reduced barrier compared to CH_4 (relative in each case to their respective σ-adduct precursors).[30] Recent work by Gunnoe and Cundari supports this idea with computed C–H activation barriers at a {TpRu(PH_3)(CH_3)} fragment following the trend CH_3NO_2 < CH_3CN < $(CH_3)_2CO$ < THF < *c*-C_6H_{12}. Moreover a less basic acceptor group (CH_2CN in place of CH_3) increases the barrier. All these observations are consistent with a degree of heterolytic character in the transition states associated with these late transition metal SBM processes, with C–H activation resembling an intramolecular proton transfer.[31]

2.2. SBM at L_nM–boryl bonds

The success of the catalytic alkane hydroborylation[4] has prompted a number of computational studies on the mechanism of this process.[14] The C–H activation step has been studied by Hall for [CpFe(CO){B(OMe)$_2$}(CH_4)] and [CpW(CO)$_2${B(OMe)$_2$}-(CH_4)].[32] Both systems proceed by what Hall calls a "metal-assisted-SBM" with rather short M···H contacts of 1.50 Å (Fe) and 1.75 Å (W). A localised orbital analysis, however, has been interpreted in terms of very little oxidative character in the transition state. Instead the transferring H is protonic in nature and the reaction is assisted by the electron pair of the M-B bond. A Mulliken charge analysis suggests that this process is itself supported by back donation from the metal into the vacant p-orbital on boron, **4**. Similar conclusions were found for methane activation step at {CpRh(H)(BO_2R)} R = –CH_2CH_2–.[33]



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2.3. SBM at L_nM=CR_2 and L_nM≡CR bonds

Hall has stressed the isolability of the {L_nM–BR_2} and {L_nM=CR_2} moieties[33] and has studied C–H activation in [CpW(NO)(CH_2)(CH_4)] and [CpW(CO)(CH_2)(CH_4)]$^-$ species. Intriguingly, pathways corresponding to both a one-step SBM and a two-step OA/RE mechanism can be characterized for these systems (Fig. 5). For the nitrosyl species, SBM is slightly more accessible, while OA/RE is preferred with the anionic CO analogue.[34] The major geometric differences between the SBM transition state and OA/RE intermediate are in the C–W–C angles (40–50° wider in the OA intermediate) and W···H distances (*ca.* 0.1 Å shorter in the OA intermediate). More recently, activation of sp^2 and sp^3 C–H bonds by 1,2-addition across a titanium alkylidyne (M≡C) has been reported. DFT calculations suggested a SBM-like transition state.[35] More detailed calculations showed that there was a degree of polarisation in the transition state and the process corresponds to a heterolytic splitting of the C–H bond.[36] The behaviour of this M≡CR species is similar to that seen with M–OR/NR_2 systems (see below) and may reflect the presence of occupied orbitals on the accepting ligands in each case. For the M≡C systems this takes the form of occupied π-bonds, whereas the heteroatomic species have lone pairs available. By analogy, M=CR_2 species should show similar behaviour.

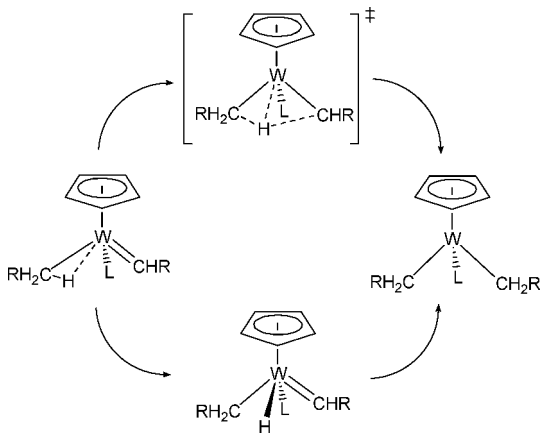


Fig. 5 Two step OA/RE (bottom) and one-step SBM (top) computed for H-transfer in [CpW(L)(CH_2)(CH_4)] systems (L = CO$^-$, NO).

2.4. Overview

The above discussion highlights the range of late transition metal L_nM–C/B systems where computation shows SBM to occur. Several of the research groups active in this field have

proposed mechanistic interpretations of these processes and the area is now awash with acronyms. Computational studies have focused on the nature of the transition state, thus OATS (Lin), OHM (Goddard) and MASBM (Hall). In addition, Perutz and Sabo-Etienne have proposed the σ-CAM (σ-complex-assisted metathesis) mechanism, based on the experimental observation of reactant and product E–H σ-complexes. E is most commonly H, SiR_3 or BR_2, but in principal this idea extends to C–H σ-complexes.[37] Hall has used the atoms-in-molecules (AIM) approach[38] to characterise different transition states in terms of the varying patterns of bond critical points (BCP) and ring critical points (RCP) (see Fig. 6).[39] Hall assigned these to transition states for (from left to right) SBM (computed for $[Cp_2Sc(CH_3)(CH_4)]$ and $[Pt(acac')_2(Ph)(C_6H_6)]^+$), MASBM ($[Pt(acac')_2(CH_3)(CH_4)]^+$), OATS/σ-CAM ($[Ir(acac')_2(C_2H_4Ph)(C_6H_6)]$, OA/RE ($[Cp^*Ir(PMe_3)(CH_3)(CH_4)]^+$) and OHM ($[Ir(acac')_2(CH_3)(CH_4)]$). This last pattern is also seen for an intermediate formed *via* OA (*e.g.* ($[Cp^*Ir(PMe_3)(CH_3)H(CH_3)]^+$).

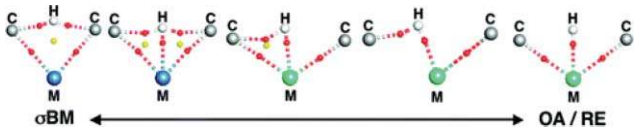


Fig. 6 Spectrum of mechanisms for metal-mediated C–H activation processes showing BCPs (red) and RCPs (yellow). Reproduced with permission from ref. 39. Copyright 2007, American Chemical Society.

Despite this elegant outcome, it seems likely that a continuum of transition state structures will be formed as more computational data become available on SBM processes. Indeed Hall refers to a 'spectrum of mechanisms for metal-mediated hydrogen transfer' and other workers have emphasized this in their work.[16,23] This continuum is already apparent in the range of Ru···H distances reported by Gunnoe and Cundari. In addition, a common feature of these SBM processes is that C–H activation involves a degree of heterolytic character and therefore proton transfer. Subtly 'different' mechanisms can therefore correspond to a different source of stabilization for this proton (electrons from the metal centre or from the acceptor M–ligand bond) or the degree of substrate acidity/acceptor group basicity. In this context, it is interesting to note that recent calculations on the SBM reactions of CH_4 with $[Cp_2M–Me]$ species (M = Sc, Y, La, Ce, Sm, Ho, Yb and Lu) are characterised by polar transition states with near-linear $\{Me^{\delta-}\cdots H^{\delta+}\cdots Me^{\delta-}\}$ moieties that suggest a proton transfer process.[40] As with late transition metal systems, C–H activation is computed to become more accessible when a more acidic hydrogen is transferred.[41]

A final issue concerns the relative accessibility of OA/RE *vs.* SBM in late transition metal systems. In several cases discussed above SBM appears to become 'necessary' only when the metal centre is not sufficiently electron rich to achieve an OA process, or perhaps when steric factors render a more highly coordinated intermediate inaccessible. However, there are now several cases where both SBM and OA have been characterised for the same system.[34,42] As more instances of this emerge the patterns that favour one process over another will become clearer. In the meantime, computational work must be careful to consider all possible pathways before deciding that the lowest energy route has been defined.

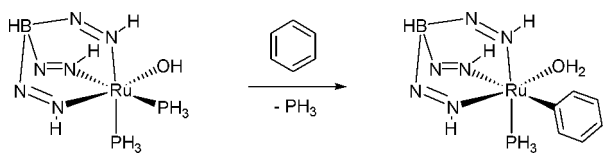
3. C–H activation at $L_nM–X$ bonds (X = O, N) (1,2-addition)

As discussed above, recent computational studies of SBM at M–C bonds suggest that these reactions can often be viewed as a proton transfer between a polarised C–H bond and a polarised M–C bond. Consistent with this idea the more polarised the starting M–C bond the faster the proton transfer. One might predict therefore that the related process in which a proton is transferred from a C–H bond to a more strongly polarised M–X bond (X = O, N) would be more facile (this process is also referred to as 1,2-addition). Another interesting question in these reactions is whether the lone pair on the acceptor atom (O, N) facilitates transfer of the hydrogen as a proton.

The earliest experimental examples of net 1,2-addition of C–H bonds to early transition metal M=X (X = O, N) double bonds were provided by the groups of Bergman[43] and Wolczanski.[44] Some of these complexes will even activate methane and computational studies of these reactions have also been reported[44b,c] (see also the discussion of the activation of sp^2 and sp^3 C–H bonds by 1,2-addition across a titanium alkylidyne (M≡C) in Section 2.3 above).

The reactions of late transition metal amides with C–H bonds has been known for some time.[45] However most early examples of this type of reactivity involve outer sphere acid–base type chemistry in which the metal plays a spectator role and the reactivity is rather similar to an alkali metal amide.[45,46] Such reactions initially lead to ion pairs; substitution of the amine by the anion may subsequently take place. To achieve the net 1,2-addition of a C–H bond to an M–X (X = O, N) bond requires a vacant site on the metal. This positions a Lewis acidic/electron deficient metal adjacent to a nucleophilic/basic heteroatom providing ambiphilic reactivity, ideal for a heterolytic splitting of a substrate bond. This process is related to the heterolytic splitting of H_2 across an M–X bond which is well established[47] and indeed plays a key role in many hydrogenation catalysts.[48,49]

The first examples of net 1,2-addition of a non-acidic C–H bond to an M–X (X = O, N) single bond were observed experimentally in 2005 by the groups of Gunnoe and Periana.[50,51] Gunnoe *et al.* first reported the C–H activation of benzene with $[TpRu(PMe_3)_2(OH)]$.[50] This complex undergoes H/D exchange with C_6D_6 at the hydroxide ligand and will catalyse H/D exchange between C_6D_6 and H_2O at 100 °C. Detailed kinetic experiments showed that the dissociation of PMe_3 was occurring prior to H/D exchange and the selectivity for H/D exchange at the *meta* and *para* positions of toluene is consistent with a metal-mediated process. DFT calculations on a model system showed that the reaction (Scheme 2) is substantially endergonic (ΔG = +18.4 kcal mol^{-1}) consistent with the final phenyl complex not being observed experimentally. Similarly, the formation of $[(Tab)Ru(PH_3)_2(Ph)]$ and water was calculated to be endergonic (ΔG = +9.1 kcal mol^{-1}).



Scheme 2

Location of the transition state gave a free energy barrier to C–H activation of +17.6 kcal mol^{-1} relative to an η^2-benzene complex intermediate. The corresponding barrier for activation of benzene by {(Tab)Ru(CO)(Me)} was calculated to be +21.2 kcal mol^{-1}.

Subsequently, Gunnoe *et al.* extended this C–H activation chemistry to [TpRu(PMe$_3$)$_2$(X)] (X = OPh, NHPh, NH$_2$, SH, Cl, OTf).[52] Of these the NHPh complex showed H/D exchange of the NH group with C$_6$D$_6$, however the complexes X = NH$_2$, SH, Cl, OTf did not undergo C–H activation (note the NH$_2$ complex decomposed under the reaction conditions).[52] They suggested that the ease of C–H activation is related to the basicity of the group receiving the hydrogen and that C–H activations at non-dative, heteroatom-based ligands coordinated to low oxidation state late transition metals would entail inherently lower activation barriers than similar reactions with metal–alkyl or aryl bonds.

In an attempt to understand more about the various factors affecting the energetics of 1,2-additions Cundari and Gunnoe carried out a more extended computational study of C–H activation by the series of complexes [(Tab)M(PH$_3$)$_2$X]^q (X = OH or NH$_2$; M = Tc or Re, $q = -1$; M = Ru, $q = 0$; M = Co or Ir, $q = +1$; M = Ni or Pt, $q = +2$).[53] The first step in the C–H activation was loss of phosphine to provide a formally 16-electron five-coordinate species which may be stabilised by π-donation by X. In this study η^2-benzene adducts were only observed for the dicationic Ni or Pt complexes (X = OH, NH$_2$) and the monocationic [Ir–OH] complex. The increased interaction between the metal and benzene correlated well with the metal acidity as judged by the computed charge on the metal, although the authors emphasise that their calculations ignored solvation effects hence charge effects may dominate. Electron deficiency at the metal may be compensated by coordination of benzene or π-donation from the amide. The hydroxo complexes have more acidic metal centres than the amido ones (NH$_2$ is a stronger base than OH based on gas phase proton affinities) hence there are more stable benzene adducts in the hydroxo series.

The transition states for benzene activation have a 4-centred geometry with an obtuse angle at the hydrogen being transferred and relatively short M–H distances (Fig. 7). However, the M-H distances are longer on average (8% for OH and 12% for NH$_2$) than the estimated M–H covalent bond lengths and AIM[38] analyses on representative structures were consistent with no M-H bond being present in the transition state. In addition, for activation of benzene by [(Tab)Ru(PH$_3$)X] (X = Me, NH$_2$, OH) there is a substantial difference in the transition states between X = Me and X = NH$_2$/OH with a much shorter M–H distance in the transition state for X = Me (Fig. 7). They ascribe this difference to the presence of the lone pair on NH$_2$/OH, thus the directed sp^3 hybrid on Me less effectively bridges the transferring hydrogen and the metal. This is similar to the selectivity for transfer of H over alkyl in SBM observed by Bercaw *et al.* in 1987,[28] and similar conclusions have been reached in computational studies.[14,54a]

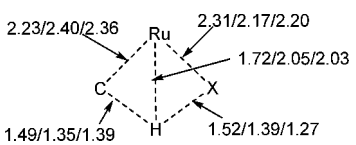


Fig. 7 Calculated metric data for C–H activation of benzene by [(Tab)Ru(PH$_3$)(X)] where X = Me, NH$_2$, OH.[53]

Cundari and Gunnoe conclude that this type of C–H bond activation is inherently more facile when the receiving atom is anionic and heteroatomic than hydrocarbyl and the mechanism should be viewed as an internal proton transfer. They also note that the complexes with more electrophilic metals give earlier transition states (shorter C–H distances, longer X–H distances). Similarly, earlier transition states are computed when an NH$_2$ is the accepting ligand compared to OH, as might be expected from the higher basicity of the former. The M–X distances in the transition states are closer to the products than to the active 16-electron species which they ascribe to a more significant contribution to the C–H activation from the ligand than from the metal. It is interesting to note that if the metal is made more electrophilic, by oxidation, the nature of the C–H activation chemistry can be radically altered. Thus, oxidation of [TpRu(PMe$_3$)$_2$(OH)] by AgOTf gives [TpRu(PMe$_3$)$_2$(OH)]OTf, which can abstract hydrogen atoms from relatively weak C–H bonds *e.g.* forms benzene from 1,4 cyclohexadiene.[55]

Periana *et al.* showed that [Ir(acac′)$_2$(OMe)(L)] (L = MeOH, pyridine) reacts with benzene at 160 °C to produce an Ir–Ph complex and that use of C$_6$D$_6$ led to formation of CH$_3$OD.[51] The reaction is insensitive to added oxygen and CH activation of toluene only occurs in the *meta* and *para* positions consistent with a non-radical process. Calculations were interpreted in terms of a reaction proceeding *via* a SBM-type process rather than oxidative addition. The complexes also catalyse H/D exchange between D$_2$O and C$_6$H$_6$ presumably *via* an Ir–OH species and this was subsequently verified experimentally.[56] Experiments in the presence of added pyridine, and comparison of the kinetic isotope effect (KIE) for reaction of [Ir(acac′)$_2$(OH)(Py)] with a mixture of C$_6$H$_6$ and C$_6$D$_6$ ($k_H/k_D = 1.07 \pm 0.24$) with that for 1,3,5-trideuteriobenzene ($k_H/k_D = 2.65 \pm 0.56$), are consistent with rate determining coordination of benzene followed by faster C–H activation. Calculations accurately model the KIE and show that the reaction is energetically favourable ($\Delta G = -6.8$ kcal mol$^-$1) and that the transition state for C–H cleavage is only 6.7 kcal mol^{-1} higher than the benzene adduct.

More recently, Oxgaard *et al.* carried out a detailed orbital analysis of the mechanism of the C–H activation step in the reaction of [Ir(acac′)$_2$(OMe)(Py)] with benzene and concluded that the forming O–H bond is not based on the same orbital as the breaking O–Ir bond.[57] The transition state is similar to that for [(Tab)Ru(PH$_3$)(OH)] (Fig. 7) with a C···H distance of 1.29 Å slightly shorter than that, 1.39 Å, for the Ru^{II} complex, consistent with an earlier transition state for the more electrophilic Ir^{III}. The analysis is not consistent with a traditional SBM mechanism but rather with an activation of the C–H bond by an electrophilic metal generating a positively charged hydrogen, which is then transferred to the metal-bound hydroxide *i.e.* to an internal base. Hence, they used the term internal electrophilic substitution (IES) to describe the mechanism. They note the similarities with heterolytic activation of dihydrogen[47] and with an asymmetric sigmatropic rearrangement. Interestingly, changing the nature of X in [Ir(acac′)$_2$(X)(C$_6$H$_6$)] (X = OMe, OCF$_3$, NH$_2$) has very little effect on the activation energy barriers (less than 2 kcal mol^{-1}).[57] In contrast, for the model system [(Tab)Ir(PH$_3$)X(C$_6$H$_6$)] the difference in $\Delta G^{\ddagger}$ is 11.3 kcal mol^{-1} between X = OH and NH$_2$ with the barrier being lower for OH.[53]

Whilst there is no doubt that the electrophilicity of the metal is playing an important role in the C–H activation, the term IES does not perhaps convey the extent to which the heteroatom lone pair plays a role in the activation of the C–H bond. Indeed, as suggested by Gunnoe and Cundari[53] the C–H activation is easier in the case of X = OH than X = Me; they also emphasise the significant contribution to C–H bond scission from the ligand.

In conclusion, the net 1,2-addition of C–H bonds to an M–X bond (X = O, N) occurs *via* a 4-centre transition state. However, there is no M–H bonding interaction and the forming X–H bond is not based on the same orbital as the breaking M–X bond. Thus, these processes are fundamentally different to conventional SBM and involve a concerted ambiphilic electron-deficient metal and basic ligand acting together to cause a heterolytic scission of the C–H bond. For further discussion see below.

4. "Electrophilic" C–H activation at late transition metals mediated by carboxylate or carbonate bases

Theoretical calculations have also offered insights into "electrophilic" type C–H activations. So-called Shilov chemistry has been known since 1969 and has been reviewed.[2,58] Such chemistry has been the subject of a number of computational studies and the C–H activation step has been modelled as oxidative addition or an electrophilic or SBM mechanism, aided by inter- or intramolecular base.[59–61] In this section we will concentrate on the more recently studied systems of "electrophilic activation" of C–H bonds which involve carboxylate or carbonate as base. Parallels with Shilov type chemistry will be made where appropriate.

4.1. Intramolecular C–H activation

Cyclometalated complexes of the platinum metals were first reported in 1965.[62] The facile cyclometalation by palladium acetate, particularly of N-donor ligands had been well studied experimentally in the 1980s and 1990s. Ryabov had proposed that cyclopalladation of dimethylbenzylamine occurred by an electrophilic substitution *via* a Wheland intermediate with subsequent intramolecular deprotonation by coordinated acetate *via* a 6-membered transition state (Fig. 8, **5**).[63] Detailed mechanistic studies, including volume of activation measurements, suggested a highly ordered transition state. Similar studies on cyclopalladation of imines led Gomez to propose a related mechanism but with a highly ordered 4-membered transition state for intramolecular deprotonation (Fig. 8, **6**).[64] Such a process would be closely related to the 1,2 additions discussed in Section 3. Distinguishing between these two possibilities by experiment is virtually impossible, however DFT calculations can shed light on the dilemma.

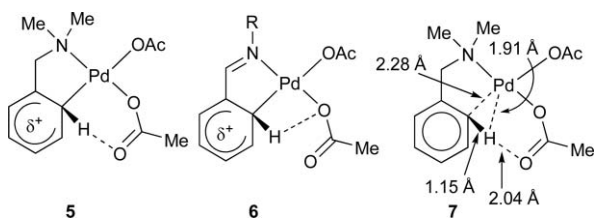


Fig. 8 Proposed transition states (**5**, **6**).[63,64a] and calculated agostic intermediate (**7**) in cyclometalation of dimethylbenzylamine by $[Pd(OAc)_2]$.[65]

Davies and Macgregor published the first computational study of these processes in 2005.[65] The calculations on [Pd(DMBA-H)$(OAc)_2$] (DMBA-H = dimethylbenzylamine) located an intermediate in which an acetate arm has been displaced by one *ortho*-C–H bond of DMBA-H. The interaction between the electrophilic Pd^{II} centre and the C–H bond was more consistent with an agostic structure, rather than a Wheland intermediate formed by electrophilic attack on the π-system (Fig. 8, **7**). In addition, the agostic interaction, although rather weak (Pd···C and Pd···H distances of 2.28 and 1.91 Å, respectively), is sufficient to polarize the C–H bond and allow acetate to form an intramolecular hydrogen bond to the transferring hydrogen. Thus, the process is best viewed as an ambiphilic activation, by an electrophilic metal centre and an intramolecular base. The rate-determining step is computed to be formation of the agostic intermediate *via* the κ^2–κ^1displacement of acetate. Subsequent intramolecular deprotonation occurs with a minimal energy barrier (<1 kcal mol^{-1}). C–H activation *via* the 6-membered transition state was shown to be more favourable than the type of 4-membered transition state suggested by Gomez, although both these processes were considerably more favourable than an alternative oxidative addition of the C–H bond followed by reductive elimination of acetic acid. Interestingly, the central role of an agostic intermediate suggests that C–H activation in such systems may not be limited to aryl C–H bonds and this has proved to be the case (see below).

Subsequently, Davies and Macgregor showed that cyclometalation of DMBA-H with $[Cp^*_2IrCl_2]_2$ in the presence of sodium acetate occurred by a very similar mechanism. Calculations on the model intermediate, $[CpIr(DMBA\text{-}H)(\kappa^2\text{-}OAc)]^+$, (Fig. 9, **8a**) showed the 6-membered transition state to give **9a** was favoured over a 4-membered process *via* **8b** to **9b** or oxidative addition to an Ir^V species, **9c**.[66] In this case, unlike palladium, no intermediate agostic complex was observed on the calculated reaction path. The main activation energy barrier again seems to be related to converting a κ^2-acetate to κ^1 and once this is done there is essentially no barrier to C–H activation. The importance of the intramolecular hydrogen bonding in the activation was further

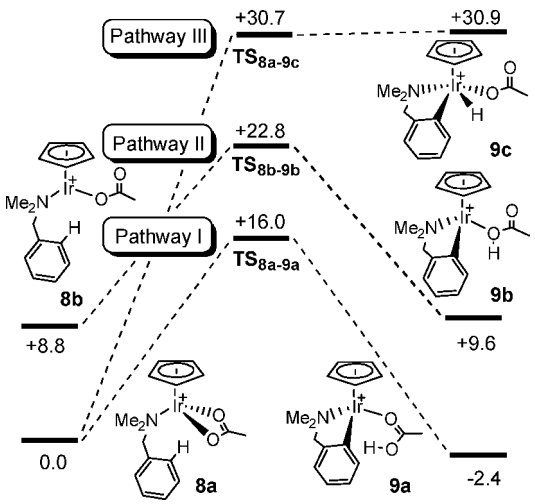
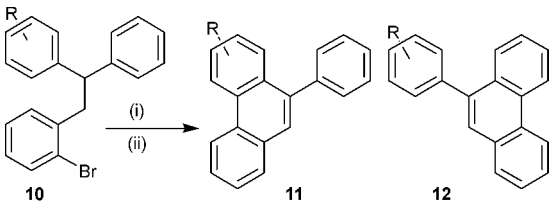


Fig. 9 Computed reaction profiles (kcal mol^{-1}) for C–H activation in $[Ir(DMBA\text{-}H)(OAc)Cp]^+$. **8**. Pathway I is *via* a 6-membered transition state, Pathway II *via* 4-membered transition state and Pathway III by oxidative addition.[66]

demonstrated in the preference for N-H activation over C–H activation in cyclometallation of a pyrrole imine.[67]

Related base-assisted cyclometallation reactions have also been incorporated into schemes for Pd-catalysed intramolecular arylation. These reactions typically involve initial oxidative addition of an aryl C–Br bond with cyclometallation occurring at a pendant substituent of the resultant M–aryl ligand. Echavarren, Maseras and co-workers reported an early combined experimental and theoretical study of such a process, where **10** reacted to give either **11** or **12**, depending on the substituents, R (Scheme 3).[68] Their experimental studies suggest the key step to be a C–H activation in which the hydrogen from the phenyl is transferred as a proton, rather than *via* an electrophilic aromatic substitution mechanism.



(i) $Pd(OAc)_2$, L, K_2CO_3, DMA, 135 °C (ii) DDQ

Scheme 3

Originally, the authors favoured an initial exchange of bromide (generated by C–Br oxidative addition), by bicarbonate. This then allowed the C–H cleavage to occur through a 6-membered transition state with strong hydrogen bonding between the proton being transferred and the bicarbonate (Fig. 10 **TS 10C**) with a calculated energy barrier of 23.5 kcal mol^{-1}. An alternative 4-membered transition state with bromide as the acceptor (**TS 10A**) (*c.f.* intramolecular transfer to chloride in Shilov chemistry)[59] had a rather higher energy barrier of 43.3 kcal mol^{-1}. In their later full paper[69] the authors gave further consideration to a mechanism in which the bicarbonate is not bound to the palladium but still assists the C–H cleavage step by intermolecular hydrogen bonding (**TS 10B**) (*c.f.* intermolecular transfer to chloride in Shilov chemistry).[60] The calculated energy difference between an inter- and intra-molecular proton abstraction was at most 6 kcal mol^{-1}, but which was the favoured pathway depended on the substituents on the ring being activated. The calculations accurately reproduce the trends in reactivity, *i.e.* electron-acceptor substituents in the ring being activated favour the reaction to give **11**, while electron-donating substituents drive the reaction to the unsubstituted ring (*i.e.* formation of **12**, Scheme 3). In a further study[70] these workers showed that bidentate phosphines are excellent ligands for this process and concluded that at least in this case the reaction

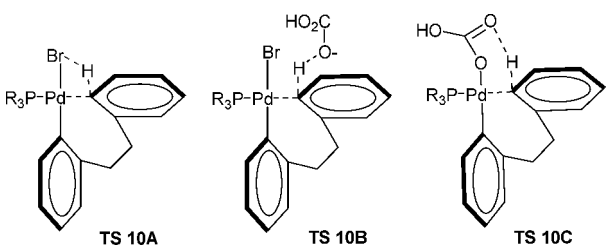
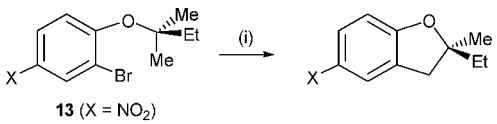


Fig. 10 Schematic transition states for aryl C–H bond activation, modelling intramolecular arylation of **10**.[68]

proceeds by an intermolecular base-assisted proton abstraction mechanism.

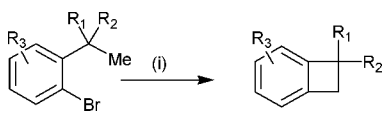
Similar strategies have allowed the activation of sp^3 C–H bonds to be exploited in synthesis. Fagnou *et al.* investigated the reactions of substrates such as **13** (Scheme 4) and calculations again show concerted palladation/intramolecular proton abstraction *via* 6-membered transition states. The computed results also correctly reproduce the observed selectivity *i.e.* formation of a 6-membered palladacycle by activation of a primary C–H bond (**TS 13A** $\Delta G^{\ddagger}$ = 27 kcal mol^{-1}) is favoured over formation of 6-membered palladacycle by secondary C–H activation (**TS 13B** $\Delta G^{\ddagger}$ = 32.5 kcal mol^{-1}) or formation of a 7-membered palladacycle by activation of a methyl (**TS 13C** $\Delta G^{\ddagger}$ = 33.1 kcal mol^{-1}), respectively.[71] The transition states all feature an agostic interaction between the activating C–H bond and palladium in combination with hydrogen bonding to the acetate.



(i) $Pd(OAc)_2$, PCy_3-HBF_4, Cs_2CO_3, pivalic acid mesitylene, 135 °C

Scheme 4

Baudoin, Clot *et al.* also studied sp^3 C–H activation in the formation of benzocyclobutenes (Scheme 5).[72] Even in this case with formation of a strained 4-membered ring C–H activation is still the rate limiting step as confirmed by a KIE of 5.8. Surprisingly, the computed product of initial C–Br oxidative addition (Fig. 12, **14**) has phenyl *trans* to phosphine and bromine *trans* to the vacant site whereas in [Pd(Ph)(Br)(P^{t}Bu$_3$)] characterised crystallographically by Hartwig *et al.*[73] Br is *trans* to phosphine with aryl opposite



(i) $Pd(OAc)_2$, P^tBu_3, K_2CO_3, DMF, 140 °C

Scheme 5

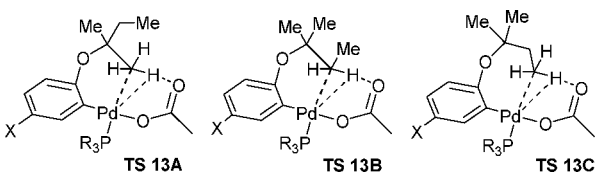


Fig. 11 Schematic transition states for sp^3 C–H activation in intramolecular cyclisation of **13** (X = H).[71]

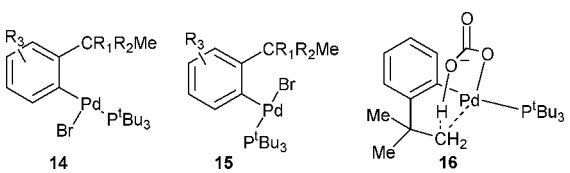


Fig. 12 Proposed oxidative addition products and subsequent transition state for sp^3 C–H activation in intramolecular cyclisation to form benzocyclobutenes (see Scheme 5).[72]

the vacant site (Fig. 12, **15**). Calculations confirm that the X-ray isomer (**15**) is more stable by 6.5 kcal mol^{-1}.

Calculations of the substitution of Br in **15** by various bases yielded (κ^2-O_2CX)Pd complexes (X = Me, OH, O^-) which give rise to transition states for C–H activation analogous to those found by Fagnou[71] (Fig. 11); however the activation energy barriers ($\Delta E^{\ddagger}$) are rather higher (33–45 kcal mol^{-1} compared with 27.0 kcal mol^{-1}) and C–H activation is computed to be strongly endothermic. The trends in computed $\Delta E^{\ddagger}$ (acetate lowest, carbonate highest) are also completely opposite to those found experimentally. Computation of C–H activation from the other isomer (**14**) proceeds *via* (κ^1-O_2CX)Pd complexes, which, in contrast with the bromo complex **15**, have a clear agostic interaction with one C–H bond on the ^{t}Bu group on the aromatic ring. Proton transfer from C(sp^3) now occurs in a plane perpendicular to the P–Pd–Ph axis (Fig. 12, **16**). The $\Delta E^{\ddagger}$ values are much lower (27.5–29.2 kcal mol^{-1}), the reaction is computed to be exothermic and the greater reactivity of carbonate is now correctly modelled. Thus, these calculations demonstrate that the carboxylate/carbonate does not need to be located *cis* to the site being activated in the square plane.

Computational studies of such direct arylation reactions are not limited to palladium. Maseras, Dixneuf and co-workers studied ruthenium-catalysed arylation of 2-phenyl pyridine.[74] They concluded that the most likely mechanism involves proton abstraction by coordinated bicarbonate, however in this case the proton is transferred to the metal bound oxygen *via* a 4-centre transition state.

4.2 Intermolecular C–H activation

The Pd(II) catalysed coupling of benzene with an alkene *via* a C–H activation was demonstrated experimentally by Fujiwara as long ago as 1967.[75] This reaction and others have traditionally been thought to proceed by an electrophilic aromatic substitution. In 2000 Sakaki carried out a theoretical study at the MP4(SDQ) level on the activation of benzene and methane by [M(η^2-$O_2CH)_2$] (M = Pd, Pt) and [M($PH_3)_2$].[76] He concluded that [M($PH_3)_2$] cannot easily achieve C–H activation but that [M(η^2-$O_2CH)_2$] can because the formate ligand assists the C–H bond activation through formation of a strong O–H bond. Key geometric parameters for the computed intermediate (**17**) and transition state (**18**) for benzene activation with [Pd(η^2-$O_2CH)_2$] are shown in Fig. 13. The reactions go *via* intermediates in which a C–H bond displaces one arm of a bidentate acetate and the C–H bond that is broken lengthens significantly in the transition state. An electron distribution analysis showed that in the C–H activation the atomic population of M significantly increases while that of H remarkably decreases. These data are consistent with an heterolytic fission of the C–H bond in which electrophilic attack of M to benzene or methane occurs concomitantly with the proton abstraction by the carboxylate ligand. These transition states are very similar to those computed for formate assisted heterolytic activation of dihydrogen by a ruthenium catalyst.[77]

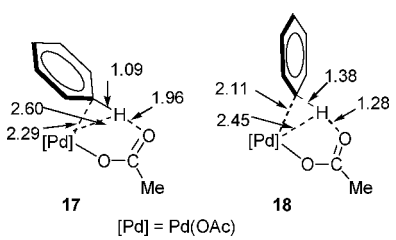


Fig. 13 Calculated metric data for the intermediate and transition state computed for the activation of benzene by [Pd(OAc)$_2$].[76] Distances in Å.

In 2006 Fagnou *et al.* reported[78] the catalytic direct arylation of perfluorobenzenes.[79] Experimentally they showed that the reaction was favoured for electron deficient arenes *i.e.* a complete reversal of selectivity in comparison with electrophilic aromatic substitution. Computational studies showed that the reaction proceeds *via* a concerted arene metalation and C–H bond cleaving process which depends directly on the acidity of the C–H bond being cleaved. The lowest energy pathway was computed to be transfer of the proton to Pd-bound bicarbonate *via* a 6-membered transition state (*c.f.* **TS 10C** in Fig. 10). As seen in Maseras' work, transfer to coordinated bromide (*c.f.* **TS 10A**, Fig. 10) was a higher energy alternative. Fagnou used the term concerted metalation deprotonation (CMD), which also emphasises the dual role of metal and (intramolecular) base. In this case a pathway involving intermolecular deprotonation by external bicarbonate could not be located. Later, Fagnou *et al.* showed the experimental benefit of adding pivalic acid, and calculations suggested pivalate had a slightly lower (1.3 kcal mol^{-1}) transition state energy than bicarbonate.[80] We have shown that for intramolecular deprotonation variation in the pK_a of the base has only a rather small effect on activation energy barriers since the base strength is somewhat reduced by coordination to the metal.[81]

Interestingly, in a more wide-ranging study of direct arylation reactions across a broad range of aromatic substrates Gorelsky and Fagnou[82] were unable to find any evidence for Wheland-type intermediates but instead found the lowest energy route to involve 6-membered transition states in which very little charge builds up on the aromatic ring. This is a very similar pattern to that found in cyclometallation reactions.[65] This pathway correctly predicts the regioselectivity for all the arenes studied regardless of their electronic properties. An activation-strain analysis showed that π-electron rich aromatics have the most favourable interaction with the metal (most negative E_{int}) values but that these are offset by the highest energetic cost of distorting the catalyst and arene from the ground state to the transition state geometries. Electron deficient arenes have less favourable E_{int} but a more facile arene distortion so the transition state remains accessible. Benzene is not favoured by either value and has the highest $\Delta E^{\ddagger}$ of the arenes evaluated. Overall they concluded that this type of mechanism may be more widespread than previously thought in direct arylation reactions and may apply even to electron rich aromatics previously assumed to go *via* electrophilic aromatic substitution.

Periana *et al.* have recently compared C–H activation by K[Pt(pic)(TFA)$_2$] (pic = picolinate) **19** and Pt(bpym)(TFA)$_2$ (bpym = 2,2′-bipyrimidyl) **20** and considered the effect of the charge on the complex on the overall C–H activation process.[83] The calculated $\Delta H^{\ddagger}$ for C–H activation of benzene by complex **19** was 21 kcal mol^{-1} (experimental activation barrier for H/D exchange between C_6H_6 and CF_3CO_2D was 23 kcal mol^{-1}), significantly lower than the value for the bpym complex **20** of 27 kcal mol^{-1}. The C–H activation occurs in two steps, κ^2–κ^1 displacement of one TFA and coordination of the arene and then activation of the C–H bond. For complex **20**, the ΔH for the first step is 14 kcal mol^{-1} with the subsequent C–H cleavage step having an activation

barrier, $\Delta H^{\ddagger}$, of 13 kcal mol^{-1}. For complex **19**, the ΔH for the first step, displacement of an anionic TFA from the anionic complex, is much easier than from the neutral one at ~5.0 kcal mol^{-1} and the $\Delta H^{\ddagger}$ for C–H cleavage shows only a slight increase to ~16 kcal mol^{-1}. Thus the main difference in overall rates of H/D exchange for these complexes (TOF for complex **19** is about 300 times that for **20**) is due to more favourable coordination of benzene, with the overall C–H cleavage step being relatively unaffected by the overall increase in negative charge of the complex.

In a recent study, Ess *et al.* have carried out a transition state energy decomposition study of C–H activation of benzene and methane by [Ir(acac′)$_2$(X)] (X = OAc and OH).[84] Hydroxide can only act as an intramolecular base with a 4-membered transition state (see Fig. 14, **21**; this process is termed ES by this group) but acetate can have a 4-membered or 6-membered transition state (Fig. 14, **22** and **23**, respectively). As found previously,[65,66] C–H activation *via* 6-membered **23** is favoured over **22**, for both benzene and methane activation by about 20 kcal mol^{-1}, it is also favoured by about 15 kcal mol^{-1} over **21**. The authors conclude the most significant contribution to the energy difference between **23** and **22** is the energy required to deform the reactants into their transition state geometries. For activation of benzene in **22** the C–O bond lengths of the acetate are rather different at 1.35 and 1.21 Å, changing these to 1.25 and 1.28 Å, respectively, (as found in the 6-membered transition state) lowers the fragment distortion energy by ~13 kcal mol^{-1}. The authors also point out that the transition states for the hydroxide and 4-membered acetate are very similar, indeed we feel these should be considered as the same process (see below).

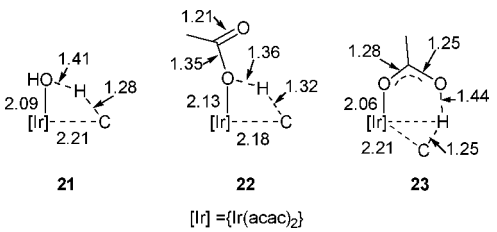


Fig. 14 Comparison of key metric data in transition states for the activation of benzene with {Ir(acac′)$_2$(X)}. Distances in Å.[84]

5. Overview of heteroatom-assisted C–H activation

Since 2000, several computational studies have shown that the combination of an electrophilic metal and a lone pair on an internal base, either metal-bound (4-membered) or pendant (6-membered) can lead to the concerted ambiphilic activation of C–H bonds. Davies and Macgregor also commented on the possible synergic effect of the two components.[67] Thus, interaction of the C–H bond with the electrophilic metal makes the C–H bond more acidic which in turn facilitates hydrogen bonding from the heteroatom lone pair. It is now easy to rationalise the great success of carboxylates, as well as bicarbonate and carbonate (and possibly phosphate) in palladium catalysed reactions involving a C–H activation step as being in large part due to their ability to act as an intramolecular base.[65] In some cases, however, it is possible that such bases act in an intermolecular fashion.[69,74] In passing, it is worth noting the resemblance between the 6-membered ring transition states discussed here and those associated with Noyori's transfer hydrogenation catalysts.[85] This also involve metal–ligand bifunctional cooperativity,[48,86] and calculations[87] have shown that transfer of the hydrogen from the alcohol to the catalyst occurs *via* a cyclic 6-membered transition state.

As pointed out in Section 3, C–H activation at M-X bonds (X = O, N) involves little, if any, M–H bonding interaction. Moreover, the forming X–H bond is not based on the same orbital as the breaking M–X bond. Thus, these processes are fundamentally different to conventional SBM at M–H, M–C and M–B bonds. In this regard C–H activation reactions at M–X bonds can then be considered as another variant of a concerted ambiphilic activation, where an electron-deficient metal and a basic ligand cause the heterolytic scission of a C–H bond.

The term internal electrophilic substitution (IES) has been suggested for C–H activation of benzene at an Ir–OH bond (see **21**, Fig. 14). However, in our opinion this does not convey the extent to which the heteroatom lone pair plays a role in the activation of the C–H bond. It is the concerted dual activation that make these processes different from a conventional electrophilic process and why their selectivity is different to conventional electrophilic aromatic substitution. The term concerted metalation deprotonation (CMD) has been used by Fagnou and this certainly emphasises the dual nature of the process. However, given that recent studies on SBM suggest these also have polarised transition states and can therefore be thought of as involving deprotonation, we feel it would be useful to distinguish concerted ambiphilic activations from SBM. Hence we propose that such processes should be termed ambiphilic metal ligand activations (AMLA), essentially showing that there must be an available "lone pair" on the ligand, with the number of atoms involved in the transition state, where known, listed in parentheses. Thus, in Fig. 14, **21** and **22** correspond to AMLA(4) processes and **23** is an AMLA(6).

6. Conclusions

The last decade has seen great progress in the information that computational chemistry can provide about reaction mechanisms, information that would otherwise be extremely difficult, if not impossible, to obtain by experiment. In particular, mechanistic subtleties abound in the field of C–H activation. SBM processes are now recognized to be accessible in a much wider range of metal complexes than previously, but delineation from OA reactions can only be routinely achieved computationally. Close collaboration between experiment and computation has provided a much better understanding of C–H activations at M–X bonds (X = O, N) and those mediated by carboxylate or carbonate bases. This powerful synergy has facilitated the discovery of new catalysts where C–H activation can be exploited in synthesis. Heteroatom-assisted C–H activations are particularly prominent in these developments and the common features of such processes appear to be the simultaneous ambiphilic activation by a Lewis acidic metal centre and an intramolecular base. We therefore suggest use of the acronym AMLA (ambiphilic metal ligand activation) for such reactions.

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