Historical Perspective invited for Shilov Special Issue

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A. E. Shilov's Influence on Early Work in Organometallic CH Activation and Functionalization

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Abstract

The work of A. E. Shilov was a key factor in the development of the area of CH activation and homogeneous catalysis of alkane conversion to functionalized products with transition metals. In this account, the early developments of the field up to the mid 1980s are covered to illustrate this influence, in particular on our own work.

1. Introduction

This account treats the early development of homogeneous organometallic CH activation with transition metals, emphasizing the period up to the early 1980s so as to illustrate the influence of A. E. Shilov (1930-2014)[1-2] on the development of the area, particularly in relation to our own work. Shilov's work itself is reviewed in this issue by his close associate, A. A. Shteinman, and the state of advancement of his work in the mid 1980s, can be gathered from Shilov's 1984 monograph.[3]

Some definitions may be useful as a starting point for the discussion. The term CH activation typically refers to a step in which a C—H bond is replaced by a

C—M bond in a reaction with a metal reagent or catalyst. This may then be followed by a functionalization step in which the C—M bond is converted to a C—X bond in the final product, X being any desired organic substituent such as a halide or a hydroxy group.[3] Another common functionalization step is β -elimination of an intermediate alkylmetal species leading to an unsaturated final product.[4-6] In some cases, a catalytic functionalization proved possible.[7] A contemporary review of the state of the whole organometallic alkane activation field in the mid 1980s is also available.[8]

2. The Early Period

Late *d* block elements were the focus of the earliest work. Indeed, organometallic CH activation goes right back to 1898, when Dimroth reported the mercuriation of benzene with $\text{Hg}(\text{OAc})_2$ to give PhHgOAc . [9-10] In 1931, Kharasch extended this strategy to auration.[11] The selectivity of these and related methods follows the general pattern of electrophilic aromatic substitution[12a] and for a very long time CH activation by mercury compounds was confined to arenes. Periana and coworkers have only much more recently extended this work to alkanes, however, with a report of the efficient catalytic oxidation of methane to methyl bisulfate at 180°C catalyzed by mercuric ions in 100% H_2SO_4 , where the acid acts both as solvent and as oxidant.[13a]

In the form of organolithium[14] and Grignard reagents[15], *s* block elements can also metallate activated CH bonds, even sp^3 ones, but nearby functional groups are generally needed. These can enhance the reactivity, and thus govern the selectivity, by acidifying nearby CH bonds. Alternatively, prior metal binding to a functional group on the substrate can enhance the reactivity of nearby CH bonds by chelation control, as in the case of directed lithiation of arenes.[16] Catalysis by *p* block elements, arising from incorporating a subsequent functionalization step into a full catalytic cycle, is a relatively little-explored field with great future promise. In a striking recent example, I^+ in oleum catalyzed

methane conversion to methyl bisulfate at 195°.[13b] Elements from the *f* block, still rarely encountered in the CH activation field, may also repay closer study.[17]

3. Later Developments

The contributions of *d* block transition metals to organometallic CH activation began in the 1960s with cyclometallation, then moved to intermolecular chemistry in the 70s, went on to gain wider recognition in the 80s and 90s, and retains its interest right up to the present.[13c,18] These studies soon went beyond arenes and activated *sp*³ CH bonds to tackle the harder problem of the activation and functionalization of alkanes and of unactivated CH bonds in locations remote from any existing functional groups. The key novel point in the intermolecular case was that the selectivity pattern that emerged is unlike that seen for any of the standard organic pathways. To take the case of propane, Hg(OAc)₂ is not sufficiently reactive to touch it at all, and organic pathways that go by reactive radicals or electrophiles often show a preference for attack the secondary position to give *i*-PrX products (X = metal or a functional group derived from a subsequent functionalization step). The highest primary/secondary per-bond selectivity ratio that can be achieved in standard organic reactions is the nearly 1:1 value seen for the most reactive radicals. [12b] In contrast, activation by *d* block transition metals typically gives preferential or even exclusive functionalization of the least substituted CH bond, in the case of propane for example, to give *n*-PrX products.[8,19] This selectivity pattern, already apparent in Shilov's early results,[3] was not only an indication of a new mechanism at work but also provided a potential path to a variety of desirable *n*-alkyl derivatives from cheap *n*-alkane as starting material.

An early goal was to functionalize unactivated CH bonds, particularly in alkanes as the least reactive class of CH-containing substrates. Later extension to complex organic compounds posed the problem of selective functionalization of unactivated CH bonds remote from existing functionality. Although many such methods are now known,[20-28] we are still far from having solutions adapted to

every major compound class and every important type of functionalization, and new aspects continue to be reported on a regular basis.

3.1 Cyclometallation

The first organometallic reaction type, cyclometallation, a term that dates from 1973,[29] was already common enough by 1977 to be the subject of a detailed review with more than 150 cited references.[30] The very earliest example even goes back to the late 1950s.[31] Cyclometallation proved to be much more common for aryl CH bonds than for aliphatic ones. Even though these CH bonds are stronger than aliphatic ones, they are kinetically more reactive and the resulting arylmetal bonds are substantially stronger than alkylmetal ones.

Shaw showed how introducing bulk into the ligand set could favor cyclometallation even in the case of an aliphatic CH bond (eq. 1).[32] This can be considered as an inorganic extension of the Thorpe-Ingold effect,[12c] by which gem-dimethyl substitution greatly favors ring formation in organic chemistry. While eq.1 is indeed an alkyl CH activation, this CH bond cannot therefore be considered as truly unactivated with the chelate effect providing additional encouragement for the ring formation.

(1)

3.2 Chatt's work

Joseph Chatt (1914-1994)[33] is often credited with being the first to apply traditional *d* block organometallic methods to the problem of intermolecular CH activation of hydrocarbons without reliance on chelate assistance. As early as 1964, working with Davidson at the Imperial Chemical Industries Research Center at Runcorn (UK), he saw oxidative addition of a naphthalene CH bond to the Ru atom

of an intermediate Ru(0) phosphine complex, $[\text{Ru}(\text{dmpe})_2]$, formed on reduction of the Ru(II) precursor shown in eq. 2.[34]

(2)

Activation of $\text{R}-\text{H}$ to give $\text{R}-\text{M}$ or $\text{R}-\text{M}-\text{H}$ is generally only considered as the first step on the way to full functionalization of a $\text{C}-\text{H}$ bond to give a $\text{C}-\text{X}$ group. Indeed, Chatt decomposed the naphthylruthenium adduct with DCl to give the free monodeuterated naphthalene in the subsequent functionalization, if we can properly apply that term to an isotope exchange. Although arenes were reactive, the somewhat less reactive thf solvent did not react in the Chatt system and alkane substrates were not considered viable at that time. Perhaps because he moved in 1964 to head the Unit for Nitrogen Fixation (UNF) at Sussex University, Chatt became fully engaged with the nitrogen fixation problem[35] and did not continue work in CH activation. In an interesting parallel, Shilov also became very interested in nitrogen fixation during the same period,[36] although this did not lead him to abandon the alkane problem.

At the UNF, where I was a graduate research student, the Unit personnel came together at the daily afternoon teas, leading to wide-ranging conversations, both ephemeral and substantial. At one of these, prompted by the rapid advances being made in the early 1970s, Chatt was asked, possibly only as a joke, what we would do if the nitrogen fixation problem were to be solved. Apparently taking the question seriously, however, he said he might then redirect attention to the CH problem as the most worthy goal for the institute. Naturally, I made a mental note of this point for future development in my independent work.

3.3 Hodges and Garnett

The next advance came in a series of papers dating from 1967-69 by Hodges and Garnett at the University of New South Wales, who reported H/D exchange between AcOD and various arenes, catalyzed by $\text{Na}_2[\text{PtCl}_4]$. In their 1967 work,[37] no substrates were chosen where attack at an alkyl group could have been securely demonstrated. Given the methods then available, their MS data only told them the *number* of deuteriums incorporated in the substrate and so they could only suggest plausible locations for the deuteration. With $\text{Ph}(t\text{-Bu})$ as substrate, for example, a maximum incorporation of only three deuteriums was seen, leading to the proposal that these D atoms were located at the arene meta and para ring positions, with the implication that the ortho ring positions were sterically blocked by the *t*-butyl group and that the *t*-butyl group itself was untouched.

Among the arenes studied in Hodges and Garnett's 1969 paper,[38] however, were PhEt , $\text{Ph}(i\text{-Pr})$ and $\text{Ph}(n\text{-Pr})$, where the alkyl groups did become partially deuterated, as shown by the maximal deuterium incorporation exceeding the number of aryl CH sites. For example, up to 8 D atoms were incorporated into PhEt , meaning that both the benzylic CH_2 and the terminal methyl group must have been involved. NMR spectroscopy, still a somewhat exotic technique in 1967, had by 1969 become available for determining the positions of deuteration. It then became clear that the α and β alkyl positions of PhEt were being deuterated at almost identical rates. In retrospect, this might have suggested that alkanes could perhaps react with Pt(II) in the same way. At the time, however, direct interaction of Pt(II) with the alkyl chain was presumably thought to be out of the question. In any event, the authors initially adopted a mechanism in which the Ph-Et carbon-carbon bond oxidatively added to the metal and the resulting Ph-Pt-Et group underwent the isotope exchange, followed by reductive elimination of the labeled ethylbenzene. The mechanism was later revised after ^{14}C isotope studies led to the conclusion that C-C bond breaking did not occur, leaving π -benzyl species as the most likely intermediates.[39] No attempts to look at alkane substrates were reported in the

1969 paper, however. This omission was consistent with the then-current understanding that cyclometallation was restricted aryl groups, intermolecular alkane CH activation was not therefore considered.

3.4 Shilov Chemistry

The next, crucial step was taken by Shilov and colleagues at the Institute of Chemical Physics at Chernogolovka, close to Moscow. In a 1969 article,[40] they showed that an alkane, in this case CH₄, was also a viable substrate for the Pt(II) H/D exchange catalyst. In this early report, the authors cite the Garnett and Hodges work as the reason for choosing the Pt(II) catalyst. Also in the 1969 paper, CoH₃(PPh₃)₃ was reported as an active catalyst for H/D exchange for CH₄ but neither the Co system nor any related complexes were followed up subsequently because "much more definite results" were obtained with the Pt(II) catalyst. The Co complex was originally chosen because it releases H₂ reversibly, suggesting that H₃C-H might plausibly react in the same way. This cobalt result was nevertheless a precursor to all the extensive CH activation chemistry later catalyzed by phosphine complexes, notably of iridium, work that continues right up to the present.[41]

Later work on linear alkanes gave selectivity information, from which two points of special interest emerged. The most striking was the preference for isotope substitution at the terminal site of an alkane chain. This is contrary to the secondary CH₂ > primary CH₃ selectivity pattern seen for all the classic organic electrophilic and radical reactions. This nonstandard selectivity gives organometallic alkane activation its special value, a point first established in Shilov's work.

The second unexpected point was the early appearance of multiply exchanged products, implying that the alkanes typically suffered multiple exchange steps during a single encounter with the metal. The concept of alkane complexes and sigma complexation in general was only to be developed long in the future, so the most plausible proposed intermediates were alkenes from C₂ and higher alkanes but carbenes were required to explain multiple exchange in methane.[42] These

results only became clearer mechanistically when alkane sigma complexes[43] were found to bind tightly enough to permit multiple isotope exchanges.

In a key later development, alkane functionalization was extended beyond H/D exchange to C—Cl bond formation.[44] This proved possible with $[\text{PtCl}_6]^{2-}$ as oxidant, retaining Pt(II) in its catalytic role. The important aspect of this work was the appearance of the same prim. $\text{CH}_3 > \text{sec. CH}_2$ selectivity pattern in chlorination as was seen in the isotope exchange. This opened the way to the later work, notably by Periana, on the oxyfunctionalization of methane with a number of catalysts, including ones based on Pt. [45]

Having been alerted by Chatt and Green to the importance of CH activation, I followed Shilov's work closely but was surprised that it was not taken up elsewhere in this period. A number of factors may have been responsible. The CH activation topic had not yet gained any high profile in the chemical world in the early 1970s. Halpern, an influential physical organic chemist of the period, published a 1978 paper on irreversible reductive elimination of alkanes from $\text{cis-}[\text{Pt}(\text{R})(\text{H})(\text{PR}_3)_2]$ complexes.[46] From the fact that the reaction was both thermodynamically favorable and had a low barrier, he argued that "This conclusion is of some significance in the context of the widespread current interest in the catalytic activation of saturated hydrocarbons and suggests that oxidative addition (at least with such mononuclear complexes) is not a promising approach." This was a particularly unsettling paper for me because we were already obtaining apparently positive results in our own CH activation work and the Halpern caveat naturally raised the possibility that we were being misled in some way. There was also beginning to be a concern that some supposedly homogeneous reactions were in fact catalyzed by heterogeneous catalysts, which would have to be Pt colloids in the Shilov case.[47-48]

3.5 M. L. H. Green

If C—H oxidative addition was the pathway that led to Shilov chemistry, it seemed as if it might be possible to isolate R-[M]-H containing products from a

suitable [M] and R-H ([M] = unsaturated metal complex). Malcolm Green, my mentor as an Oxford undergraduate research student, published a series of papers on this problem. From 1970, he reported the photolysis of Cp_2WH_2 in various solvents that also acted as substrates.[49-50] Indeed, the proposed Cp_2W intermediate, formed after photoextrusion of H_2 , proved able to insert into a variety of aromatic and aliphatic C—H bonds. In the earliest work, arenes proved effective (eq. 3) but even aliphatic cases were viable, the least activated case being SiMe_4 (eq. 4). This success can easily be reconciled with Halpern's argument in that the photon energy, by eliminating H_2 from the complex, generates a high energy intermediate for which the alkyl CH oxidative addition is no longer contrathermodynamic. The Halpern caveat might therefore still have been held to apply to thermal reactions.

(3-4)

3.6 Alkanes as Ligands

A related question that emerged in the 1970s was to what extent could alkanes act as ligands. Already in 1968, Trofimenko[51] proposed that an intramolecular C-H...M interaction was present in an $\text{Et}_2\text{B}(\text{pz})_2$ (pz = pyrazolyl) molybdenum complex, where the C-H bond in question was part of an ethyl substituent on boron. In their work on matrix-isolated and solution phase metal carbonyls, Turner, Burdett, Perutz and Poliakoff were able to show that photoextrusion of CO led to formation of reactive unsaturated fragments such as

$\text{Cr}(\text{CO})_5$ and $\text{Fe}(\text{CO})_4$, which bonded weakly but intermolecularly to alkanes and even to Xe.[52]

Alkane complexation is relevant to the activation problem in that alkane complexation is proposed as the event that can subsequently lead either to oxidative addition (eq. 5, upper branch) or to loss of a proton (eq. 5, lower branch). In either case a metal alkyl complex $[\text{M}]\text{R}$ is formed from the alkane, RH , thus achieving the activation step. Shilov chemistry seems more likely to proceed via proton loss rather than oxidative addition, but rapid proton loss from a transient oxidative addition product cannot be excluded.

3.7 Oxidative Addition of Alkane CH Bonds

Simple alkanes only proved amenable to a photolysis-induced oxidative addition strategy somewhat later with the work of the groups of Bergman,[53] Jones[54a] and Graham[55] from 1982 onward. For example, photolysis of $\text{Cp}^*\text{Ir}(\text{PMe}_3)_2\text{H}$ in the presence of a wide variety of alkanes gave rise to a highly reactive $\text{Cp}^*\text{Ir}(\text{PMe}_3)$ fragment that attacks the alkane solvent to give the oxidative addition product $\text{Cp}^*\text{Ir}(\text{PMe}_3)(\text{R})(\text{H})$ (eq. 6). With the detailed studies on the mechanism, particularly by Bergman and by Jones, the reaction arguably became the best understood transition metal organometallic reaction at that time. Again the selectivity pattern primary $\text{CH}_3 >$ secondary CH_2 differed from the classic pattern in organic chemistry. Jones[54b] work indicates that this is because the primary metal-carbon bond is stronger than the secondary metal-carbon bond by more than the difference in the C-H bond strengths that need to be broken. Thermal exchange reactions between $\text{Cp}^*\text{Ir}(\text{PMe}_3)(\text{R})(\text{H})$ and $\text{R}'\text{H}$ proved viable, both as a

demonstration of the possibility of thermal generation of the same active intermediate, $\text{Cp}^*\text{Ir}(\text{PMe}_3)$, and as a means of establishing thermodynamic and kinetic parameters for the overall reaction. Jones' article in the present special issue describes some of this work.

(6)

3.8 Our entry into the field

While I was working in the UNF (1970-73), Jack Garnett gave a talk on $\text{Pt}(\text{II})$ catalyzed H/D exchange with a title that included the phrase 'interaction with alkanes'. The advertisement for this talk excited much anticipatory interest in the UNF because most of us were not yet familiar with Shilov's work. The suggestion was even made that the title must have been a typographical error for 'interaction with alkenes'. That errors of this type are not so rare is shown by my own experience. When I gave a talk at Los Alamos National Lab that was supposed to be titled 'A New Type of Hydrogen Bond', [56] it was rendered on the published notice as 'A New Type of Hydrogen Bomb', obviously a term with which the administrative staff were much more familiar.

From 1973 to 1977 I was a postdoctoral worker then Attaché de Recherche at the Gif-sur-Yvette Natural Products Lab run by the Centre Nationale de la Recherche Scientifique. I was very fortunate to work with Hugh Felkin, on a variety of catalytic problems. He was a physical organic chemist already celebrated for the Felkin model of carbonyl 1,2 asymmetric induction. [57] At first we looked at Rh for asymmetric hydrogenation, then a very new field. Our ligands were not sufficiently effective, even by the lax standards of those days, and so I moved to standard hydrogenation and hydroformylation work.

At this stage a new doctoral student, George Morris, joined us and Felkin and I thought that he might like to look at the iridium analogues of our Rh catalysts with

the idea that the supposedly more sluggish Ir might allow isolation of interesting intermediates in the hydrogenation. Morris found that under the right conditions, notably in a non coordinating solvent, CH_2Cl_2 , the Ir compounds were very much superior to the Rh ones, particularly for hindered substrates. In addition, unlike the Rh case, the Ir system was not air-sensitive, a property now understood as arising from the Ir(III/V) cycle adopted in contrast with the Rh(I/III) cycle of the classic Rh catalysts, Rh(I) typically being an air-sensitive state.[58-59] We subsequently developed the hydrogenation chemistry that has since proved broadly useful.[60] Morris and I often chatted about science and in 1977, just as he was leaving Gif, we discussed the possibility that reversal of the hydrogenation reaction, in principle possible according to standard reversibility arguments, might provide a means to dehydrogenate alkanes. From Gif, Morris himself went on to a successful industrial career at BP in the UK and we never worked together again.

In 1977, I applied to a number of American Universities. With the kind support of Green, Chatt and Felkin, I gained an Assistant Professorship at Yale but before I moved there, Roald Hoffmann paid an extended visit to the Gif Institute and had individual discussions with some of the junior scientists including myself. Learning that I had the Yale job, he made the point that I would have to do something "pretty spectacular" to get tenure at Yale. Since I had had no contact with the American system up to that time, this was a useful tip that strengthened my inclination to look at the alkane problem as top priority. Combining my prior contact with the CH activation work of Chatt, Garnett, Green and Shilov with my current hydrogenation catalysis work with Felkin and my discussions with Morris and Hoffmann, I thought a reverse hydrogenation approach to the alkane problem would be best.

My first year at Yale (1977-8) was problematic because it turned out that no new inorganic graduate students entered in that year. A physical organic student, Jennifer Quirk, bravely decided to join, even though she would be alone in the group. Not only did she pioneer all the successful lines that later got me tenure, but she also persuaded a big group of students to join our group in the following year.

I initially attempted to turn Shilov-like Pt(II) catalysts of various sorts into alkane dehydrogenation catalysts by reversing hydrogenation. Since alkane dehydrogenation is thermodynamically uphill, cyclopentane and cyclooctane seemed promising substrates: they might dehydrogenate all the way to cyclopentadienyl (Cp) and 1,5-cyclooctadiene (cod) and provide us with a stable Cp and cod final products with the disadvantage that catalysis could not be expected if the binding of the dehydrogenation product were strong. Having no success with Pt(II), I looked around for other strategies. Since our Ir catalysts were among the most active known, it seemed to me that they might also be best for the reverse case—alkane dehydrogenation. Quirk, who was working with iridium on a different project, was eager to take on this problem and by early 1979 she had promising results.

From $[\text{IrH}_2(\text{PPh}_3)_2(\text{Me}_2\text{CO})_2]\text{BF}_4$, she initially obtained high yields of the expected dehydrogenation product, $[\text{CpIrH}(\text{PPh}_3)_2]\text{BF}_4$, but only from cyclopentene. With pure cyclopentane itself, however, Jennifer obtained only ~5% yields—not enough to publish but enough to give us confidence to continue. To improve the reaction we next tried to add a hydrogen acceptor to drive the process. We thought the acceptor should have a high heat of hydrogenation but be a poor ligand, to prevent it from binding strongly to the metal and preventing the alkane from accessing the active site. Quirk finally identified neohexene ($t\text{-BuCH=CH}_2$) as the right choice and with that alkene we obtained results that were published at the end of 1979 (eq. 7). [4]

In a phone call shortly after submission, George Whitesides revealed himself as a referee for our first paper. He pointed out that on closer study, striking results like ours' could easily prove misconceived. Was I sure I had eliminated the possibility of heterogeneous metal as the true catalyst? This was the same objection that Shilov in particular had had to meet. Was I sure the alkane was pure? Since I was an Assistant Professor, he no doubt felt benevolent and passed the paper for publication after I said that I had "no reputation to lose" and that we had done our best to avoid these problems but would be very unhappy if we were scooped simply because we had not published.

3.9 Catalytic Alkane Dehydrogenation

As early as 1983, Felkin, who had naturally taken a close interest in our progress, was the first to show homogeneous catalytic alkane dehydrogenation using our *t*-BuCH=CH₂ acceptor but with a rhenium polyhydride, [ReH₇(PAR₃)₂], as catalyst. The C₆, C₇ and C₈ cycloalkanes were all converted to the cycloalkenes in up to 9 turnovers at 30-80°.[7] Our own first catalyst, reported in 1985, was [IrH₂(CF₃CO₂)(PCy₃)₂](Cy = cyclohexyl), a complex closely related to our stoichiometric system, but with a CF₃CO₂ anion as ligand. This anion was initially chosen to permit alkane-solubility without permanently blocking the open sites at the metal needed for catalysis since chelating κ²-CF₃CO₂ should be able to open up to become a monodentate κ¹ unit. This complex successfully catalysed the thermal dehydrogenation of cyclooctane with *t*-BuCH=CH₂ as acceptor. The novel point here was our photochemically driven catalytic dehydrogenation with release of H₂ in which the photon energy (254 nm) drives the process, removing the need for a hydrogen acceptor.[61] The acceptorless thermal dehydrogenation, in which reflux of the solvent drives loss of H₂, only came about much later with Fujii and Saito's work of 1990.[62] In our own extension of this acceptorless dehydrogenation, the new point was finding a nonprecious metal catalyst, [(triphos)WH₆] (triphos = PhP{CH₂CH₂PPh₂}₂).[63]

4. Conclusion

The sequence of events covered here illustrates the evolution up to 1985 of the concepts involved. Chatt showed stoichiometric, intermolecular arene CH

activation by oxidative addition with Ru(0), a result which led to subsequent isotope exchange in a separate 'functionalization' step. Garnett and Hodges made isotope exchange in arenes catalytic with Pt(II) and even found isotope exchange in the side chains of alkyl-substituted arenes. Shilov made the crucial extension to simple alkanes, where he found both isotope exchange and true functionalization with Pt(II). We were able to bring about stoichiometric alkane dehydrogenation with a hydrogen acceptor alkene, $t\text{-BuCH=CH}_2$, to drive the process and Ir-based complexes related to our previous hydrogenation catalyst. After Felkin's catalytic dehydrogenation with $t\text{-BuCH=CH}_2$, a number of Ir catalysts were found, but the acceptorless version was only developed later, at a time beyond the scope of the present survey. Even today, we still lack a desirable level of generality and tunable selectivity in the known reaction set, so the qualities of innovation and initiative shown by Shilov continue to be needed.

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