



## Review

## Organometallic alkane CH activation

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**Abstract**

The title topic is reviewed with emphasis on catalysis and on recent advances. Alkane  $\sigma$  complexes, Shilov chemistry and oxidative addition routes are covered. Attention is also given to  $\sigma$  bond metathesis, surface-bound organometallics and CH activation involving carbene complexes. Closely related reactions of non-alkane substrates such as the Murai reaction are also discussed. © 2004 Elsevier B.V. All rights reserved.

**Keywords:** Alkane functionalization; Oxidative addition;  $\sigma$  Bond metathesis

Some areas of science have a fertile period in which the topic moves quickly to a resolution after which interest moves on to other problems. In contrast, while the CH activation area has had its share of notable advances, the central problem is still unsolved. There is still no series of general, selective, efficient catalytic functionalization reactions of unactivated  $sp^3$  CH bonds. Many of the separate elements of a solution seem to be in hand, or at least in sight, but bringing them together has so far eluded the community. Since this is a 40th Anniversary special issue, the historical roots of the field are sketched out in Section 2. This is particularly appropriate since organometallic CH activation dates from 1962, only anticipating the founding of this journal by a year.

**1. Introduction**

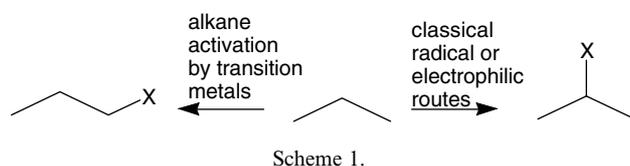
Activation is considered to be the binding of a substrate to a metal center. This can be followed by a functionalization step in which the substrate is transformed. Ideally, the starting metal species is regenerated and cy-

cle is catalytic. The term ‘CH activation’ [1] emphasizes the distinct reactivity pattern of low valent metal complexes from that of classical organic reagents which break CH bonds by electrophilic or radical routes. In a classical route, radicals such as  $\cdot OH$  readily abstract an H atom from alkanes, RH, to give the alkyl radical  $R\cdot$ . Included in this group are some metal catalyzed oxidations, such as the Gif reaction and Fenton chemistry [2]. Sufficiently electrophilic reagents such as superacids, abstract  $H^-$  ion from an alkane. Since the radical reaction tends to occur at the weakest CH bond, the most highly substituted  $R\cdot$  tend to be formed, for example *i*-Pr $\cdot$  and not *n*-Pr $\cdot$  from propane. Likewise, the electrophilic selectivity pattern of superacid chemistry [3] even more strongly favors the more substituted carbonium ion product such as *i*-Pr $^+$  and not *n*-Pr $^+$  from propane. In any subsequent functionalization by such classical routes, the branched product is obtained, e.g., *i*PrX and not *n*PrX (see Scheme 1).

Low valent transition metals, however, tend to insert into an alkane CH bond to give an alkylmetal hydride where the least substituted alkyl is often preferred. In any subsequent functionalization, the linear product is often obtained, e.g., *n*PrX and not *i*PrX. CH activation is potentially of practical importance in providing a route to the linear compounds that are not obtained

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by classical routes. In addition to higher alkanes, methane activation holds promise as methane seems likely to become a more important feedstock for the chemical industry. Methane conversion to methanol (or a methanol derivative such as  $\text{MeOCH}_2\text{OMe}$ ) would make a conveniently transportable fuel and also a potential new carbon source for the chemical industry. Methane-to-methanol conversion can also be carried out indirectly initial conversion to syngas ( $\text{CO} + \text{H}_2$ ) by steam reforming; this is inefficient in that methane is first over-oxidized then reduced so some of the available reducing power goes into production of water.

Partial oxidation is particularly hard in alkanes. Methanol is much more sensitive to oxidation than methane so classical oxidation procedures tend to over-oxidize the methanol to  $\text{CH}_2\text{O}$ ,  $\text{CO}$  and  $\text{CO}_2$ . The CH activation route has the advantage that the CH bond of methanol is not exceptionally reactive relative to that of methane, so the overoxidation problem, while not completely eliminated, is nevertheless less severe.

Enzymatic oxidation of methane [2] proceeds selectively to methanol with the methane monooxygenases (MMO) but the selectivity is not a function of the chemistry employed, H atom abstraction by a high valent oxoiron cluster, but of the ‘chemical engineering’ of the site. The monooxygenase pathway automatically delivers only  $2e$  of oxidation power after which the hydrophobic site expels methanol before the site is reactivated for the next oxidation to occur. This step occurs by provision of  $2e$  of reducing power that serves to reduce one O atom of the  $\text{O}_2$  substrate to water, leaving the remaining oxygen atom available for transfer to the substrate – hence the term monooxygenase. Once again some of the reducing power is ‘wasted’ to form water. Since these reactions do not occur via organometallic but via coordination compounds as intermediates, we do not discuss them further, except to provide a reference to a recent book [2] on the topic of enzymatic oxidation and its functional model compounds. We cover reactions of  $\text{sp}^3$  CH bonds with low valent transition metals that avoid radical or electrophilic selectivity patterns. A number of non-alkane CH activation reactions are included where they relate to the alkane work.

## 2. From Pauling to Chatt

Like so much else in modern chemistry, the roots of the ideas that led to organometallic CH activation can



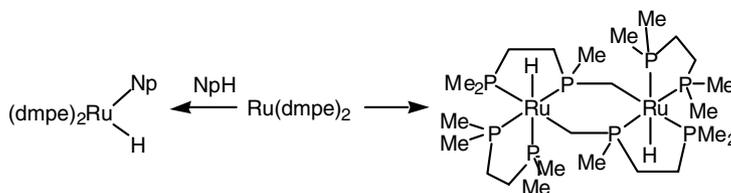
be found in Pauling’s 1939 book, *The Nature of the Chemical Bond* [4]. Pauling proposed that the short Ni–C bond in  $\text{Ni}(\text{CO})_4$  was best explained on the basis of a substantial contribution of a  $\text{Ni}=\text{C}$  double bonded resonance form (Scheme 2). Langmuir [5] had suggested a  $\text{Ni}=\text{C}$  formulation as early as 1921, but the idea was not generally accepted at the time.

In 1950, Chatt [6] argued that  $\text{PF}_3$  should act like CO in forming  $\text{Ni}(\text{PF}_3)_4$  and in stabilizing zerovalent metals by  $\text{Ni}=\text{P}$  double bonding. The idea of multiple M–L bonding was developed by Dewar for  $\text{Ag}^+(\text{C}_2\text{H}_4)$  [7] and substantiated experimentally by Chatt for Pt(II) olefin complexes [8] in what soon became the Dewar–Chatt model. Among other pieces of evidence, Chatt showed that the dipole moments of Pt(II) olefin and  $\text{PF}_3$  complexes were not consistent with simple lone pair donation according to the Werner coordination theory, but required ligand-to-metal back donation as well. As testimony to its influence, this paper has been cited over a 1000 times.

Building on these ideas, Chatt [9] postulated in 1958 that alkyl phosphines might also be able to stabilize zerovalent metals. To illustrate this he made zerovalent complexes of  $\text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2$  (now called dmpe) with a wide variety of transition metals. In 1962, Chatt [10] showed that dmpe was able to give  $[\text{M}(\text{dmpe})_3]$  complexes of zerovalent V, Cr, Mo and W and  $[\text{M}(\text{dmpe})_2]$  with zerovalent Fe and Co. These were formed by reduction of the metal halides with  $\text{Na}[\text{C}_{10}\text{H}_8]$  and dmpe in thf. The 1962 paper also reported that the  $[\text{Ru}(\text{dmpe})_2]$  analog behaved anomalously, having a  $\nu(\text{RuH})$  signal in the IR spectrum. Chatt noted that “the hydride was apparently (formed) by taking hydrogen from the naphthalene”, and that the reaction was still under investigation. By 1965, NMR spectroscopy had become available, greatly facilitating study of hydrides [11].

The key point of the 1965 paper was the full description of the properties of what was expected to be the zerovalent  $[\text{Ru}(\text{dmpe})_2]$ . When made from  $\text{Na}[\text{NpH}]$  ( $\text{Np} = 2\text{-naphthyl}$ ), the naphthalene released by the reductant had evidently oxidatively added to the Ru(0) to give  $[\text{Ru}(\text{H})(\text{Np})(\text{dmpe})_2]$  (**1**). Hydride resonances were seen in the NMR spectrum for **1**, and a  $\nu(\text{RuH})$  band was seen in the IR spectrum at  $1802\text{ cm}^{-1}$ . The *cis* geometry was assigned from the dipole moment (**6D**) (Scheme 3). The identity of the CH bond that oxidatively added to the metal was determined by cleavage with DCl to yield 2-deutero naphthalene.

Chatt found that the naphthyl hydride thermally decomposed to a complex that at first seemed to be



Scheme 3.

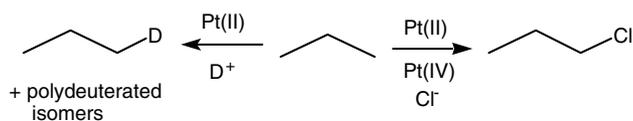
[Ru(dmpe)<sub>2</sub>], but IR signals were observed for a hydride (1791 cm<sup>-1</sup>). NMR data were not obtainable on the primitive instrument available. The proposed structure, [Ru(H)(CH<sub>2</sub>PMeCH<sub>2</sub>CH<sub>2</sub>PMe<sub>2</sub>)(dmpe)] was much later reformulated as the analogous dimer [Ru(H)(CH<sub>2</sub>PMeCH<sub>2</sub>CH<sub>2</sub>PMe<sub>2</sub>)(dmpe)]<sub>2</sub> as the result of an X-ray crystal structure (Scheme 3). This was the first cyclometallation involving an sp<sup>3</sup> CH bond.

With hindsight, we can now recognize that dmpe has limited back bonding capability, so the zerovalent metal derivatives made by Chatt have a very high tendency to give oxidative addition. In the case of Ru(0) this tendency leads to the oxidative addition even of relatively unactivated CH bonds. Today, ruthenium is still a prime choice for cyclometallation and CH activation in general, as shown by the Murai reaction discussed in Section 5.

Chatt was fully sensitized to the potential importance of CH activation and I well recall the sensation caused by the arrival in Chatt's lab of the news of Shilov's work to be discussed in the next section. This also led me to follow the Shilov work in detail in the years that followed and influenced my own choice of topic for independent work.

### 3. Shilov chemistry and alkane functionalization catalysis

Garnett and coworkers [12–15] found that H/D exchange in polycyclic aromatic hydrocarbons and heterocycles is homogeneously catalyzed by platinum(II) salts in deuterated aqueous acid medium. Exchange even occurred several carbons out along the alkyl chain of alkylaromatics, a point that led Shilov and coworkers [1,16] to extend the system to alkanes where they saw slow but definite exchange at modest temperatures. Remarkably, activation of primary CH bonds in the terminal positions of long chain alkanes was preferred (Scheme 4), in contrast with the preferential attack at

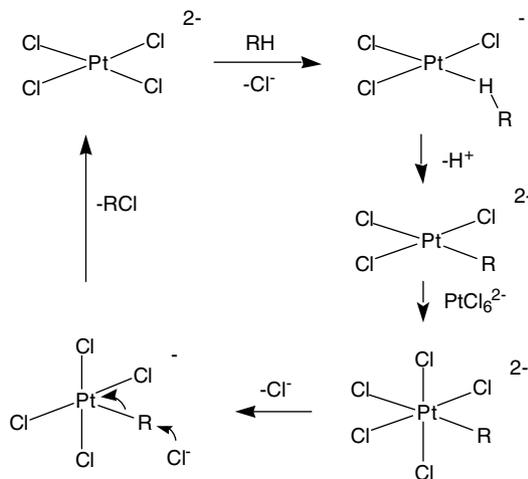


Scheme 4.

secondary and tertiary positions by classical radical and electrophilic reagents. This was the first indication of the special reactivity pattern associated with oxidative addition.

Shilov and coworkers saw alkane oxidation to ROH and RCl by moving to [Pt(IV)Cl<sub>6</sub>]<sup>2-</sup> as primary oxidant, keeping Pt(II) as the catalyst (Scheme 4). Terminal attack was still preferred with the same selectivity, so the Pt(IV) was clearly intercepting the same intermediate alkyl that led to RD in the deuteration experiments. With methane as substrate, a methylplatinum intermediate was seen [17,18]. During the 1970s, Shilov published extensively on his system but the field was otherwise quiescent. The 1980s saw a growing number of CH activation systems from a variety of research groups, with a great increase in attention to the topic and a growing awareness of the importance of the Shilov work. The state of the field at that time is reviewed in the 1984 edition of Shilov's book [18] and the present author's 1985 review [19].

Labinger and Bercaw [20] revisited the system in the 1990s using a series of mechanistic probes that confirmed Shilov's main points as well as extending the picture. Scheme 5 shows the current mechanistic view. An alkane complex either leads to oxidative addition of the alkane and loss of a proton, or the alkane σ complex loses a proton directly; only the latter possibility is shown in Scheme 5. In isotope exchange, the resulting



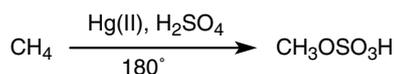
Scheme 5.

alkyl is cleaved by  $D^+$  to give RD. In the alkane functionalization, oxidation of the Pt(II) alkyl by Pt(IV) gives a Pt(IV) alkyl by electron transfer and not by alkyl transfer. The Pt(IV) now becomes a good leaving group, and  $Cl^-$  or  $OH^-$  can nucleophilically attack the R–Pt(IV) species with departure of Pt(II) to regenerate the catalyst. The origin of the unusual selectivity (methane–MeOH) is discussed in Section 6.

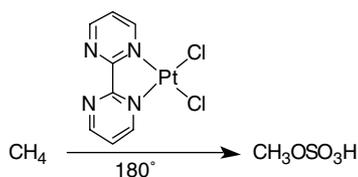
Periana et al. [21] made Shilov-like chemistry much more efficient in a series of methane conversion catalysts. With Hg(II) salts in  $H_2SO_4$  at 180, the acid is both solvent and mild reoxidant (Scheme 6). Methane was converted to the methanol ester, methyl bisulfate,  $MeOSO_3H$ , in which the  $-OSO_3H$  provides a powerful deactivating group to prevent overoxidation. At a methane conversion of 50%, 85% selectivity to methyl bisulfate (ca. 43% yield) was achieved with the major side product being  $CO_2$ . The expected intermediate  $MeHg^+$  cation was seen by NMR spectroscopy, and a Shilov-like mechanism proposed. Since Hg(II) is not expected to give oxidative addition, Hg(IV) being as yet unknown, the initial activation step must occur via deprotonation of a  $\sigma$  complex. Similar selectivity is seen for this route as for Pt(II) and indeed deprotonation of a Pt(II)  $\sigma$  complex still cannot be excluded for this case.

Periana's next development [22] was a Pt(II) catalyzed process in  $H_2SO_4$  at 180°. The metal was stabilized with a 2,2'-bipyrimidine ligand which became protonated at its free nitrogens in the acid medium. It is remarkable that the bipyrimidine remains firmly bound even in  $H_2SO_4$  at 180° (see Scheme 7). Protonation of the uncoordinated N atoms of the bipyrimidine must play a role in enhancing the stability and activity of the catalyst. Functional ligands with reversible proton transfer or redox activity have received less attention than they deserve and could well prove a fruitful field for future work.

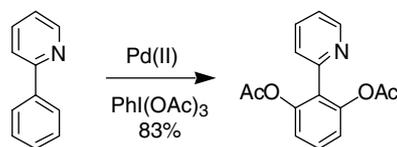
Periana et al. [23] has most recently reported direct, selective, catalytic oxidative condensation of two methane molecules to acetic acid at 180° in liquid sulfuric acid with Pd(II) salts as catalyst. Both carbons of acetic acid originate from the methane by isotope labelling.



Scheme 6.



Scheme 7.



Scheme 8.

The results are consistent with methane C–H activation to generate Pd– $CH_3$ , followed by oxidative carbonylation with methanol, generated in situ from methane, to produce acetic acid. Sen [24] has reported an intriguing series of catalytic systems for conversion of methane and other alkanes that are probably similar in character.

Applications of Pt and Pd-based chemistry to complex organic synthesis are beginning to appear. Sames and coworkers [25] finds that amino acids such as valine can be functionalized at their terminal  $-CH_3$  groups by conversion to  $-CH_2OH$  with Pt(II) and Cu(II) as oxidant. The aqueous medium avoids functional group protection, but 130° is required for turnover.

Sanford and coworkers [26] has found a practical Pd(II)-catalyzed method for the regio- and chemoselective oxidative functionalization of arenes at 75°–100° by a pathway that goes via cyclometallation, followed by oxidation by  $PhI(OAc)_2$  (Scheme 8). A variety of directing groups such as pyridine and imine were possible and selective transformation into esters or ethers is possible depending on the conditions. Using NBS as oxidant gave the aryl bromides.

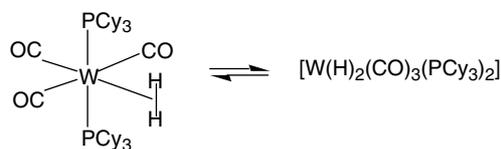
#### 4. $\sigma$ Complexes of CH bonds

The initial interaction of a CH bond with a metal center can occur without CH bond fission. Instead a C–H–M species is formed in which the CH bond acts as a 2e donor to the metal via its CH  $\sigma$  bonding electrons; hence the term  $\sigma$  complex for this general class. Where the CH bond is part of a bound ligand, such as a metal alkyl, the resulting complex is said to be agostic.

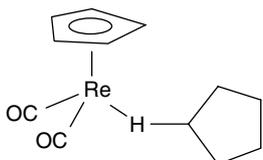
In the first recognition of an interaction between a CH bond and an unsaturated metal center, Trofimenko [27] found an example,  $[Et_2Bpz_2]Mo(CO)_2(2\text{-methylallyl}]$ , that was fully investigated by Cotton and Stanislowski [28], with a structural characterization and a fluxionality study to estimate the CH/Mo binding energy (17 kcal/mol). Brookhart and Green's review of 1983 [29] attracted wider attention to the area and introduced the term 'agostic'. Our own work [30] showed how the more tightly bound the agostic CH, the more it becomes side-on to the metal. The kinetic trajectory traced out by the CH bond in these studies matched the trajectory obtained by Cundari [31] by computational means. Other types of bonds, notably BH and SiH, were shown to be capable of becoming agostic [32].

CH activation pathways may go via an intermediate  $\sigma$  complex, one in which the alkane is bound to the metal. Such complexes [32,33] involve binding of an intact  $\sigma$  bond to a metal, of which the archetypal example is the Kubas [34]  $H_2$  complex,  $[W(H_2)(CO)_3(PCy_3)_2]$  in equilibrium with the oxidative addition product (Scheme 9). A pair of electrons in the H–H bond acts as a 2e donor to the metal and there is also some back donation from metal  $d_\pi$  orbitals into the H–H  $\sigma^*$ . Agostic species are hemilabile in that there is at least one normal metal–ligand bond and at least one C–H  $\cdots M$   $\sigma$  bonded group. The alkyl CH bond is normally a poor ligand but as part of a chelate, it can readily form a  $\sigma$  complex. Alkanes can also form  $\sigma$  complexes without the need for assistance from chelation, but these are rarely isolable. The first evidence came from  $M(CO)_6$  photolysis in an alkane matrix where formation of  $[M(CO)_5(alkane)]$  was identified by Perutz and Turner [35] in 1975. Alkane complex intermediates were proposed as to explain the scrambling and inverse kinetic isotope effects seen in a variety of reductive eliminations of alkylmetal hydride complexes [36–39]. Janak and Parkin [40] have looked into these isotope effects in detail and shown that either normal or inverse isotope effects may be observed depending on the temperature. More recently,  $CpRe(CO)_2(n\text{-heptane})$  was detected by FTIR at room temperature in heptane [41], and  $CpRe(CO)_2(\text{cyclopentane})$  (Scheme 10) was detected by NMR spectroscopy [42]. Structural evidence has been obtained for an iron porphyrin<sup>15</sup> heptane complex [43] and for a cyclohexane uranium complex [44].

C–H  $\sigma$  complex are relevant to CH activation because of the very large degree of acidification of the CH proton, which allows proton loss and formation of a metal alkyl as in the Shilov and Periana systems. The acidification results from the predominant ligand-to-metal charge transfer and minimal back donation in these species. The alkane adduct can also undergo oxidative addition to give an alkylmetal hydride. C–H  $\sigma$



Scheme 9.



Scheme 10.

complexation preferentially occurs at the least hindered CH bond for steric reasons. This may be a factor in the selectivity (primary > secondary > tertiary) shown by many CH activation reactions.

In a novel development, Bergman, Raymond and co-workers have encapsulated  $[Cp^*Ir(PMe_3)Me(OTf)]$  into a tetrahedral  $[Ga_4L_6]^{12+}$  cluster containing a large central cavity. The Ir complex is ordinarily capable of a wide variety of CH activation reactions, including catalytic H/D or H/T exchange. Within the cavity, only substrates that are small enough to be encapsulated along with the complex can react. In the decarbonylation of aldehydes  $RCHO$  to give  $[Cp^*Ir(PMe_3)R(CO)]$  and  $CH_4$ , a sharp cutoff in reactivity is found as the size of the R group increases [45]. This promising concept of carrying out reactions in confined and organized media will no doubt continue to be applied to a much wider variety of problems in the future.

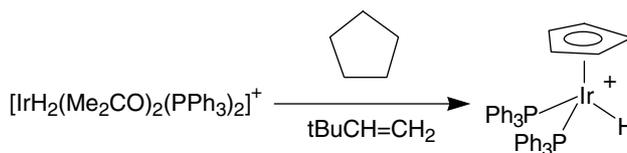
## 5. Oxidative addition and alkane conversion catalysis

Using the concept of reversing transition metal catalyzed hydrogenation of alkenes to alkanes, stoichiometric dehydrogenation of alkanes was reported in 1979 [46]. For example, cyclopentane reacts with  $[IrH_2(Me_2CO)(PPh_3)_2]^+$  to give  $[CpIrH(PPh_3)_2]^+$  with  $tBuCH=CH_2$  as 'hydrogen acceptor' (Scheme 11). Oxidative addition of an alkane CH bond was proposed as the initial step of the pathway.

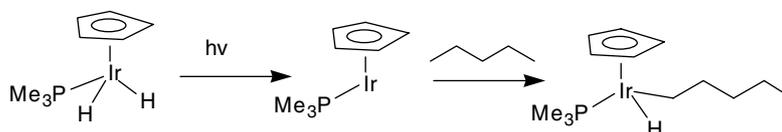
The key oxidative addition was directly observed by Janowicz and Bergman [47] in 1982, via photogeneration of  $Cp^*Ir(PMe_3)$  from the dihydride and reaction with the alkane solvent, RH, to give a variety of  $Cp^*Ir(R)(H)(PMe_3)$  species (Scheme 12).

In the minds of many observers at that time, the pre-1982 work on alkane chemistry was always tainted by a strong suspicion that the true active species was metallic Pt or Ir formed by thermal decomposition of the Pt salt or Ir complex. The chemistry of Scheme 12 not only gave us an example of the CH activation step but it led to wide acceptance of the prior work.

High selectivity was seen for attack at a terminal CH bond, analogous to Shilov chemistry, providing a mechanistic link with the prior Pt work. Strong CH bonds, present in linear alkanes or cyclopropane or benzene were preferentially activated, suggesting that the Ir–R bond strength tracked the HR bond strength. Analogous



Scheme 11.



Scheme 12.

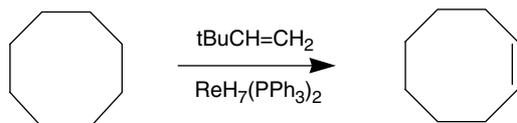
iridium carbonyls and rhodium phosphine complexes gave similar chemistry [48–50].  $\text{Cp}^*\text{Ir}(\text{R})(\text{H})(\text{PMe}_3)$  thermally eliminates  $\text{RH}$  under methane to give the very stable  $\text{Cp}^*\text{Ir}(\text{Me})(\text{H})(\text{PMe}_3)$  [51], so photolysis is not essential to success.

These are probably the most intensively studied reactions in the whole field of organometallic chemistry. Ultrafast kinetics have given evidence for the formation of intermediates such as alkane and rare gas complexes in this system [52]. Flash infrared kinetics of the photochemistry of  $\text{Tp}^*\text{Rh}(\text{CO})_2$  and  $\text{Bp}^*\text{Rh}(\text{CO})_2$  in liquid xenon solution ( $\text{Tp}^*$  = hydridotris(3,5-dimethylpyrazolyl) borate;  $\text{Bp}^*$  = dihydridobis(3,5-dimethylpyrazolyl) borate) give evidence for the formation of xenon complexes ( $\eta^3\text{-Tp}$ ) $\text{Rh}(\text{CO})\cdot\text{Xe}$  and ( $\eta^2\text{-Tp}$ ) $\text{Rh}(\text{CO})\cdot\text{Xe}$  before the formation of the cyclohexyl hydride from the cyclohexane also present. C–H oxidative addition can even be preferred over C–Cl addition, as is the case for alkyl chlorides with the  $\text{Tp}^*\text{Rh}(\text{NCR})$  fragment [53].

Felkin and coworkers [54] saw selective catalytic conversion of a variety of cycloalkanes into cycloalkenes with using  $\text{ReH}_7(\text{PR}_3)_2$  with  $t\text{BuCH}=\text{CH}_2$  as hydrogen acceptor (Scheme 13). Selective stoichiometric conversion of  $n$ -pentane into pent-1-ene was achieved by a stepwise route via the diene complex [55]. Several alkane dehydrogenation catalysts were soon found [56–58], although some lack robustness and deactivate rather readily. The buildup of alkene product naturally causes problems since this is an alternative substrate for the catalyst. To avoid  $t\text{BuCH}=\text{CH}_2$ , the reaction can either be run photochemically [59] or under reflux [60]. In each case unfavorable thermodynamics is overcome, in the first by input of light energy, and in the second by continuous removal of the product  $\text{H}_2$ .

Under irradiation,  $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$  gives catalytic alkane carbonylation [61], in which the usual alkyl hydride intermediate is believed to undergo CO insertion, followed by reductive elimination of  $\text{RCHO}$ . Once again, terminal selectivity is seen in linear alkanes.

Goldman and coworkers [62] has reported an acceptorless PCP pincer catalyst of Ir(III) that is among the most efficient to date for alkane dehydrogenation (Scheme 14). It has been applied to the introduction of



Scheme 13.

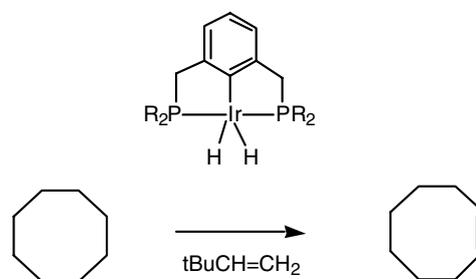
$\text{C}=\text{C}$  double bonds into aliphatic polymers [63a] and to the formation of enamines by dehydrogenation of tertiary amines [63b]. A combined computational and experimental study of bisphosphine [(PCP)IrHCl] pincer complexes has traced out the detailed pathway of the reaction [63c].

Brookhart and coworkers [64] bis(phosphinite) [(PCP)IrHCl] pincer complexes.  $\text{NaO}t\text{Bu}$  in cyclooctane (coa) with *tert*-butylethylene (tbe) as acceptor generates species with exceptional catalytic activity for the transfer dehydrogenation of coa to form cyclooctene (COE) and *tert*-butylethane (TBA). Turnover numbers up to 2200 and initial turnover frequencies between 1.6 and 2.4  $\text{s}^{-1}$  were observed at 200 °C.

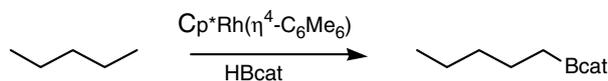
Waltz and Hartwig's [65a] transition metal-catalyzed terminal borylation of linear alkanes with  $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$  gives linear alkylboranes from commercially available borane reagents under thermal conditions in high-yield (Scheme 15). In an experimental and theoretical study in collaboration with Hall and coworkers [65b] the reaction pathway was traced, and the “unoccupied” p orbital of the dioxaboryl ligands was shown to be intimately involved in the C–H bond activation step. The hydrogen transfer to boron occurs by a boron-assisted, metal-mediated  $\sigma$  bond metathesis. The “unoccupied” p orbital of boron lowers the energy of the transition state and the intermediates by accepting electron density from the metal.

Smith and coworkers' [66] iridium catalysts are also highly effective for metal-catalyzed terminal borylation. Thanks to work on hydroboration, boranes are known to be useful intermediates to form a wide variety of derivatives, so this type of pathway could be developed into a general alkane functionalization procedure.

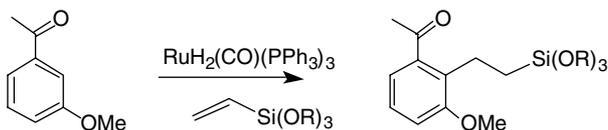
Although it is a reaction of arene rather than alkane CH bonds, the Murai reaction (Scheme 16) deserves attention. It involves the replacement of an *ortho*-CH



Scheme 14.



Scheme 15.



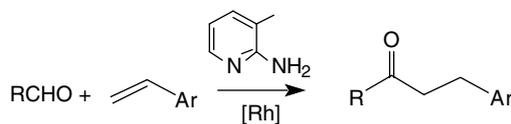
Scheme 16.

on an aromatic ketone by an alkyl group derived from an added olefin, catalyzed by Ru complexes. Cyclometallation in the first step, is followed by alkene insertion into  $\text{RuH}$  and reductive elimination of the alkylated ketone [67]. A related cyclometallation was applied to complex organic synthesis by Sames and coworkers [68] who report catalytic arylation (Suzuki reaction) and alkenylation (Heck reaction) of alkyl segments of a synthetic intermediate with  $\text{Pd}(\text{II})$ . Cyclometallation [69], has also been incorporated into a number of other catalytic reactions of organic synthetic interest [25,26,70,71], and seems capable of considerable elaboration in future. For example,  $[\text{Ir}(\text{cod})(\text{PR}_3)_2]\text{BF}_4$  and related species are catalysts of choice for the tritiation of drug molecules with chelate assisted selectivity [72].

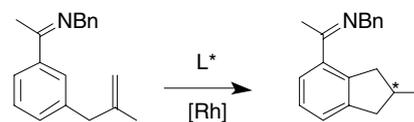
## 6. $\sigma$ Bond metathesis

When alkanes bind to metals as  $\sigma$  complexes, the net donation of charge from the  $\text{CH}$  to the metal in forming the  $\text{M}$ -alkane bond is not compensated by back donation. This is inefficient for alkanes because only one lobe of the  $\text{C-H}$   $\sigma^*$  orbital is available for back donation – the other is remote from the metal. This induces a depletion of electron density on the  $\text{CH}$  bond that acidifies the  $\text{CH}$  proton. We have already seen how deprotonation of an alkane complex has been implicated in Periana's  $\text{Hg}(\text{II})$  catalyst and cannot be excluded for Shilov's  $\text{Pt}(\text{II})$  system. Alkane acidification on binding is relevant to  $\sigma$  bond metathesis pathways of alkane activation where the alkane  $\sigma$  complex transfers a proton to a basic group such as an alkyl  $\text{M-R}'$  already present on the metal. This can lead to exchange of the  $\text{R}$  group from the  $\text{RH}$  substrate with  $\text{M-R}'$ . Watson's [73] methane exchange between  $\text{Cp}_2^*\text{LuMe}$  and  $\text{CH}_4$ , was verified with  $\text{C-13}$  methane ( $\text{C}^*\text{H}_4$ ). The oxidation state of the metal does not change, so this route is available to redox-inactive metals like  $d^0$  ions and the  $f$ -block. Indeed, Fendrick and Marks [74] found similar reactions with actinides.

In the late metals it is hard to completely eliminate the possibility of oxidative addition/reductive elimination as an alternative redox pathway to the same final



Scheme 17.



Scheme 18.

products, but Arndtsen and Bergman [75] proposed a  $\sigma$  bond metathesis pathway for the reaction of alkanes including methane with the dichloromethane complex,  $[\text{Cp}^*\text{IrR}(\text{PMe}_3)(\text{ClCH}_2\text{Cl})]^+$  with a variety of alkanes  $\text{R}'\text{H}$  to give  $\text{RH}$  and  $[\text{Cp}^*\text{IrR}'(\text{PMe}_3)(\text{ClCH}_2\text{Cl})]^+$ .

An alkane  $\text{RH}$  can also be activated by addition across a metal-heteroatom bond, as shown by Wolczanski and coworkers [76]. Sadow and Tilley [77] has seen a number of  $\sigma$ -bond metathesis reactions of methane with  $\text{Cp}_2^*\text{ScR}$  ( $\text{R}$  = alkyl).

## 7. Applications

Some useful applications of reactions involving  $\text{CH}$  activation on non-alkane substrates have attracted attention. Apart from the Murai [67] reaction, mentioned earlier, Jun and Lee [78] have described a series of hydroacylation reactions that involve the addition of an aldehyde  $\text{CH}$  bond across an olefin  $\text{C=C}$  bond, using a 2-aminopicoline as an auxiliary that reversibly forms an imine with the aldehyde, bringing it into the coordination sphere of the catalyst (see Scheme 17).

Ellman, Bergman and coworkers [79] have shown how  $\text{CH}$  activation can be applied to a series of useful transformations, such as the enantioselective cyclization of aromatic ketimines. This was achieved using  $[\text{RhCl}(\text{coe})_2]_2$  with an (*S*)-binol-derived phosphoramidite ligand. Selectivities obtained were up to 96% ee and yields were very high. The reaction even took place at room temperature for one of the optimal substrates. Coordination at the imine is followed by cyclometallation and alkene insertion (see Scheme 18).

## 8. Conclusion and future challenges

$\text{CH}$  Activation and functionalization, once exotic, has now entered the mainstream. It is routinely used in synthesis even of complex organic molecules and is likely to greatly expand in future. It would be desirable to have tunable selectivity, not just based on either

cyclometalation or terminal attack, as today. In the inorganic realm, we still need to develop a wider range of functionalization reactions to accompany the CH activation step. The latter provides a metal–alkyl bond, but these are often either inert or simply revert to alkane on attempted functionalization. Another problem is that functionalizing reagents tend not to be compatible with the alkane binding function of the catalyst – this is unsurprising since alkanes bind weakly and may be displaced by the functionalizing reagent. So far it is hard to imagine how one could design a system capable of attacking not just a site along a linear alkyl chain of, say a carboxylic acid, but be tunable to attack at different specific sites as required. Such enzyme-like selectivity will no doubt need the introduction of molecular recognition at a very sophisticated level. In spite of the strong progress to date, much work therefore still remains.

## References

- [1] A.E. Shilov, G.B. Shul'pin, *Activation and Catalytic Reactions of Saturated Hydrocarbons*, Kluwer, Dordrecht, 2000; D. Sames, personal communication, 2003.
- [2] B. Meunier (Ed.), *Biomimetic Oxidations Catalysed by Transition Metal Complexes*, Imperial College Press, London, 2000.
- [3] G.A. Olah, A. Molnar, *Hydrocarbon Chemistry*, Wiley, NY, 1995.
- [4] L. Pauling, *The Nature of the Chemical Bond*, Cornell, UP, 1939.
- [5] I. Langmuir, *Science* 54 (1921) 59.
- [6] J. Chatt, *Nature* 165 (1950) 859.
- [7] M.J.S. Dewar, *Bull. Ch. Soc. Fr.* 18 (1951) C79.
- [8] J. Chatt, L.A. Duncanson, *J. Chem. Soc.* (1953) 2939.
- [9] J. Chatt, *J. Inorg. Nucl. Chem.* 8 (1958) 815.
- [10] J. Chatt, H.R. Watson, *J. Chem. Soc.* (1962) 2545.
- [11] J. Chatt, J.M. Davidson, *J. Chem. Soc.* (1965) 843.
- [12] R.J. Hodges, J.L. Garnett, *J. Phys. Chem.* 73 (1969) 1525.
- [13] R.J. Hodges, J.L. Garnett, *J. Phys. Chem.* 72 (1968) 1673.
- [14] R.J. Hodges, J.L. Garnett, *J. Catal.* 13 (1969) 83.
- [15] J.L. Garnett, R.J. Hodges, R.S. Kenyon, *J. Chem. Soc., Perkin Trans. 2* (1979) 885.
- [16] N.F. Goldshleger, A.A. Shteinman, A.E. Shilov, V.V. Eskova, *Zh. Fiz. Khim.* 46 (1972) 1353.
- [17] L.A. Kushch, V.V. Lavrushko, Y.S. Misharin, A.P. Moravsky, A.E. Shilov, *New J. Chem.* 7 (1983) 729.
- [18] A.E. Shilov, *Activation of Saturated Hydrocarbons by Transition Metal Complexes*, Riedel, Dordrecht, 1984.
- [19] R.H. Crabtree, *Chem. Rev.* 85 (1985) 245.
- [20] J.A. Labinger, J.E. Bercaw, *Nature* 417 (2002) 507.
- [21] R.A. Periana, D.J. Taube, E.R. Evitt, D.G. Loffler, P.R. Wentreck, G. Voss, T. Masuda, *Science* 259 (1993) 340.
- [22] R.A. Periana, D.J. Taube, S. Gamble, H. Taube, T. Satoh, H. Fujii, *Science* 280 (1998) 560.
- [23] R.A. Periana, O. Mironov, D. Taube, G. Bhalla, C.J. Jones, *Science* 301 (2003) 814.
- [24] A. Sen, *Accounts Chem. Res.* 31 (1998) 550.
- [25] B.D. Dangel, J.A. Johnson, D. Sames, *J. Am. Chem. Soc.* 123 (2001) 8149.
- [26] A.R. Dick, K.L. Hull, M.S. Sanford, *J. Am. Chem. Soc.* 126 (2004) 2300.
- [27] S. Trofimenko, *J. Am. Chem. Soc.* 90 (1968) 4754.
- [28] F.A. Cotton, A.G. Stanislawski, *J. Am. Chem. Soc.* 96 (1974) 5074.
- [29] M. Brookhart, M.L.H. Green, *J. Organomet. Chem.* 250 (1983) 395.
- [30] R.H. Crabtree, E.M. Holt, M. Lavin, S.M. Morehouse, *Inorg. Chem.* 24 (1985) 1986.
- [31] T.R. Cundari, *J. Am. Chem. Soc.* 116 (1994) 340.
- [32] R.H. Crabtree, *Angew. Chem., Int. Ed.* 32 (1993) 789.
- [33] M. Brookhart, M.L.H. Green, L.L. Wong, *Prog. Inorg. Chem.* 36 (1988) 1.
- [34] G.J. Kubas, *Metal-dihydrogen and  $\sigma$ -bond Complexes*, Kluwer Academic, New York, 2001.
- [35] R.N. Perutz, J.J. Turner, *J. Am. Chem. Soc.* 97 (1975) 4791.
- [36] R.M. Bullock, C.E.L. Headford, S.E. Kegley, J.R. Norton, *J. Am. Chem. Soc.* 107 (1985) 727–729.
- [37] G. Parkin, J.E. Bercaw, *Organometallics* 8 (1989) 1172.
- [38] G.L. Gould, D.M. Heinekey, *J. Am. Chem. Soc.* 111 (1989) 5502.
- [39] W.D. Jones, *Accounts Chem. Res.* 36 (2003) 140.
- [40] K.E. Janak, G. Parkin, *J. Am. Chem. Soc.* 125 (2003) 6889, and 13219 and refs cited.
- [41] G.I. Childs, D.C. Grills, X.Z. Sun, M.W. George, *Pure Appl. Chem.* 73 (2001) 443.
- [42] S. Geftakis, G.E. Ball, *J. Am. Chem. Soc.* 120 (1998) 9953.
- [43] D.R. Evans, T. Drovetskaya, R. Bau, C.A. Reed, P.D.W. Boyd, *J. Am. Chem. Soc.* 119 (1997) 3633.
- [44] D.W. Thompson, R.M. Kretzer, E.L. Lebeau, D.V. Scaltrito, R.A. Ghiladi, K.C. Lam, A.L. Rheingold, K.D. Karlin, G.J. Meyer, *Inorg. Chem.* 42 (2003) 5211.
- [45] D.H. Leung, D. Fielder, R.G. Bergman, *Angew. Chem., Int. Ed.* 43 (2004) 963.
- [46] R.H. Crabtree, J.M. Mihelcic, J.M. Quirk, *J. Am. Chem. Soc.* 101 (1979) 7738.
- [47] A.H. Janowicz, R.G. Bergman, *J. Am. Chem. Soc.* 104 (1982) 352; R.G. Bergman, *Science* 223 (1984) 902.
- [48] W.D. Jones, F.J. Feher, *J. Am. Chem. Soc.* 106 (1984) 1650.
- [49] J.K. Hoyano, W.A.G. Graham, *J. Am. Chem. Soc.* 104 (1982) 3723.
- [50] W.D. Jones, F.J. Feher, *Organometallics* 2 (1983) 562.
- [51] M.J. Wax, J.M. Stryker, J.M. Buchanan, C.A. Kovac, R.G. Bergman, *J. Am. Chem. Soc.* 106 (1984) 1121.
- [52] J.S. Yeston, B.K. McNamara, R.G. Bergman, C.B. Moore, *Organometallics* 19 (2000) 3442, and references cited.
- [53] A.J. Vetter, W.D. Jones, *Polyhedron* 23 (2004) 413.
- [54] D. Baudry, M. Ephritikhine, H. Felkin, R. Holmes-Smith, *Chem. Commun.* (1983) 788.
- [55] D. Baudry, M. Ephritikhine, H. Felkin, J. Zakrzewski, *Chem. Commun.* (1982) 1235.
- [56] M.J. Burk, R.H. Crabtree, *J. Am. Chem. Soc.* 109 (1987) 8025.
- [57] K.C. Shih, A.S. Goldman, *Organometallics* 12 (1993) 3390.
- [58] C.M. Jensen, *Chem. Commun.* (1999) 2443.
- [59] M.J. Burk, R.H. Crabtree, D.V. McGrath, *Chem. Commun.* (1985) 1829.
- [60] T. Aoki, R.H. Crabtree, *Organometallics* 12 (1993) 294.
- [61] T. Sakakura, T. Sodeyama, K. Sasaki, K. Wada, M. Tanaka, *J. Am. Chem. Soc.* 112 (1990) 7221.
- [62] K.B. Renkema, Y.V. Kissin, A.S. Goldman, *J. Am. Chem. Soc.* 125 (2003) 7770, and refs cited.
- [63] (a) A.S. Goldman, personal communication; (b) X. Zhang, A. Fried, S. Knapp, A.S. Goldman, *Chem. Commun.* (2003) 2060; (c) K. Krogh-Jespersen, M. Czerw, N. Summa, K.B. Renkema, P.D. Achord, A.S. Goldman, *J. Am. Chem. Soc.* 126 (2004) 7192.
- [64] I. Gottker-Schnetmann, P. White, M. Brookhart, *J. Am. Chem. Soc.* 126 (2004) 1804.
- [65] (a) K.M. Waltz, J.F. Hartwig, *Science* 277 (1997) 211; H.Y. Chen, S. Schlecht, T.C. Semple, J.F. Hartwig, *Science* 287 (2000) 1995; (b) C.E. Webster, Y.B. Fan, M.B. Hall, D. Kunz, J.F. Hartwig, *J. Am. Chem. Soc.* 125 (2003) 858.

- [66] J.Y. Cho, M.K. Tse, D. Holmes, R.E. Maleczka, M.R. Smith, *Science* 295 (2002) 305;  
R.E. Maleczka, F. Shi, D. Holmes, M.R. Smith, *J. Am. Chem. Soc.* 125 (2003) 7792.
- [67] F. Kakiuchi, S. Murai, *Accounts Chem. Res.* 35 (2002) 826.
- [68] B. Sezen, R. Franz, D. Sames, *J. Am. Chem. Soc.* 124 (2002) 13372.
- [69] M.E. van der Boom, D. Milstein, *Chem. Rev.* 103 (2003) 1759.
- [70] M. Catellani, *Synlett* (2003) 298.
- [71] A.M. Echavarren, B. Gomez-Lor, J.J. Gonzalez, O. de Frutos, *Synlett* (2003) 585.
- [72] A.Y.L. Shu, D. Saunders, S.H. Levinson, S.W. Landvatter, A. Mahoney, S.G. Senderoff, J.F. Mack, J.R. Heys, *J. Label. Compd. Rad.* 42 (1999) 797;
- M. Saljoughian, P.G. Williams *Curr. Pharm. Design* 6 (2000) 1029;  
E. Clot, J. Chen, D.-H. Lee, S.Y. Sung, L.N. Appelhans, J.W. Faller, R.H. Crabtree, O. Eisenstein, *J. Am. Chem. Soc.* (in press) and references cited.
- [73] P.L. Watson, *J. Am. Chem. Soc.* 105 (1983) 6491.
- [74] C.M. Fendrick, T.J. Marks, *J. Am. Chem. Soc.* 106 (1984) 2214.
- [75] B.A. Arndtsen, R.G. Bergman, *Science* 270 (1995) 1970.
- [76] C.P. Schaller, C.C. Cummins, P.T. Wolczanski, *J. Am. Chem. Soc.* 118 (1996) 591.
- [77] A.D. Sadow, T.D. Tilley, *J. Am. Chem. Soc.* 125 (2003) 1971.
- [78] C.H. Jun, J.H. Lee, *Pure Appl. Chem.* 76 (2004) 577.
- [79] R.K. Thalji, J.A. Ellman, R.G. Bergman, *J. Am. Chem. Soc.* 126 (2004) 7192.