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C-H ACTIVATION: A FACILE PROCESS?

The article is a critical review on general concepts of C-H bond activation/functionalization, with particular reference to mechanistic and thermodynamic aspects.

Transition-metal catalysed C-C coupling reactions have undoubtedly become one of the most important reaction classes in chemical synthesis [1]. In particular, Pd-catalysed coupling reactions, most notably the Heck [2] and Suzuki [3] reaction, have been developed up to a very high degree of synthetic utility. Such reactions allow the transformation of aryl and vinyl halides into more complex organic compounds, through the substitution of the halide with an organic moiety. However, the need to use organic halides as reagents for these reactions also has some drawbacks, such as for example the co-production of salt waste. Moreover, the general applicability of these reactions has some limitations, in that it is often necessary to use organic bromides or iodides, which are more reactive but also more costly and less widely available than the corresponding chlorides. A synthetic methodology which effects the same transformation starting from simple aromatic hydrocarbons through the activation of an aromatic C-H bond would be obviously highly preferable from the point of view of both reagent cost and process cleanness.

Some example of catalytic C-H bond activation have been reported in the literature [4]. They are based on chelate-assisted oxidative addition of the C-H bond to metal centres in low oxidation state [5], or on arene metallation by electrophilic metal centres which attack the aromatic ring in a S_{EAr} reaction [6].

The basic idea of this article is to demonstrate how a good knowledge of the thermodynamics, the reaction mechanisms, the properties of ligands and metal centres can give a fundamental contribution on approaching this fascinating theme, a dream of most chemists.

In chapter 1 of the very nice book "Activation and Functionalization of C-H Bonds" (ACS) the authors write: "The carbon-hydrogen bond is the un-functional group. Its unique position in organic chemistry is well illustrated by the standard representation of organic molecules: the presence of C-H bonds is indicated simply by the absence of any other bond. This "invisibility" of C-H bonds reflects both their ubiquitous nature and their lack of reactivity. With this characteristic in mind it is clear that if the ability to *selectively functionalize* C-H bonds were well developed, it could potentially

Selected bond dissociation energies and pK_a values for C-H, H-H and O-H bonds

| RH \rightarrow R | D(R-H)/Kcal mol ⁻¹ | pK_a |
|---|-------------------------------|--------|
| CH ₄ \rightarrow CH ₃ | 104 | 40 |
| C ₂ H ₆ \rightarrow C ₂ H ₅ | 98 | 42 |
| C ₆ H ₆ \rightarrow C ₆ H ₅ | 109 | 37 |
| C ₆ H ₅ CH ₃ \rightarrow C ₆ H ₅ CH ₂ | 85 | 35 |
| C ₂ H ₄ \rightarrow CH ₂ =CH | 106 | 36 |
| C ₂ H ₂ \rightarrow CH \equiv C | 120 | 25 |
| H ₂ \rightarrow H | 104 | 25 |
| H ₂ O \rightarrow HO | 118 | 16 |

constitute the most broadly applicable and powerful class of transformations in organic synthesis" [7].

The key words are *selectively functionalize*, otherwise the answer to the question in the title would be very obvious: it is a facile process. Every smoker knows indeed how easy is to burn hydrocarbons in his lighter, in a well defined oxidation to CO₂.

If we give a look at a few *thermodynamic data* (Table), we have the first surprises: the C-H bond energies for saturated hydrocarbons are high, but lower than those of unsaturated ones like benzene, ethylene and acetylene; furthermore they are close to the H-H bond energy and lower than the O-H one. This bond energy order does not reflect at all the reactivity order, as we know that in the usual chemical conditions saturated hydrocarbons are almost unreactive. Surely other factors may be important, one of these is the acidity of the involved X-H group; at a first insight, it is evident from the data in Table that the reactivity increases with the acidity, so that water and hydrogen (pK_a 16 and 25) react very easily and unsaturated hydrocarbons (pK_a 25-37) are more reactive than the saturated ones (pK_a 40-42).

Mechanisms for C-H bond activation

This behaviour can be accounted for, if we consider the possible *Mechanisms of C-H Activation*. The classification of the various mechanisms is not unique in the literature, however three main different types of C-H activation/functionalization mechanisms can be outlined [8]:

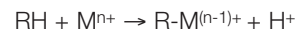
- 1) True Organometallic Activation (TOA);
- 2) Metal-through-Ligand Activation (MeLA);
- 3) Metal-Initiated Activation (MIA).

The first mechanism, TOA, involves a direct s C-M bond, resulting from the replacement of M for H in the C-H bond. This can be reached through three different ways: Oxidative Addition, Electrophilic Substitution, σ -Bond Metathesis, as sketched below:

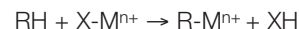
Oxidative Addition



Electrophilic Substitution



σ -Bond Metathesis



The oxidative addition requires an electron rich metal centre, which, after coordination of the hydrocarbon, must be capable of transferring two electrons on the antibonding C-H molecular orbital, so inducing C-H bond breaking and coordination of the resulting R⁻ and H⁻ fragments. The preliminary interaction of the hydrocarbon with the metal centre is of crucial importance; it justifies the easier activation of unsaturated hydrocarbons, which are better nucleophiles than the saturated ones, and, in any case, the necessity of a vacant coordination site on the metal.

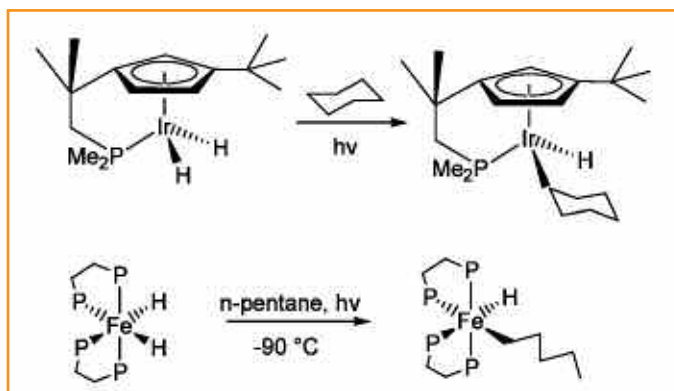


Fig. 1 - Intermolecular oxidative addition via preliminary reductive elimination of H-H or R-H

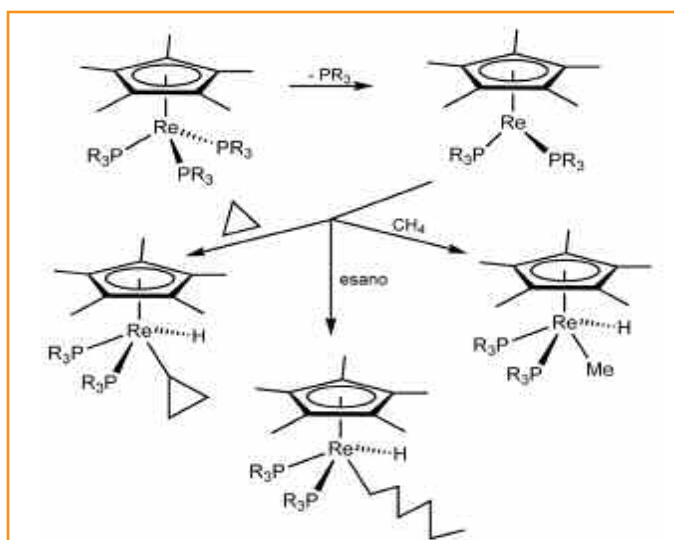
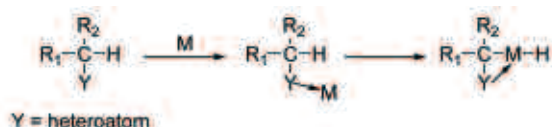


Fig. 2 - Intermolecular oxidative addition via preliminary dissociation of phosphines

Fig.s 1 and 2 illustrate nice examples of very easy *intermolecular oxidative additions* of alkanes and arenes to metal centres, coordinatively unsaturated via preliminary reductive elimination or ligand dissociation processes.

This behaviour seems to suggest that “naked” atoms should be able to activate hydrocarbons and this indeed was found under not usual reaction conditions, for example, by Schwarz and coworkers, who were able to detect CH_4 oxidative addition to Pt^+ by mass spectrometry [9], and by Basset's group using transition metals grafted on oxide supports.

In order to overcome the difficulties related to the C-H-metal interaction, a different synthetic approach involves *intramolecular oxidative addition*, which can be favoured by anchoring the hydrocarbon to the metal through a donor atom as shown below:



The high local concentration of the C-H group makes its activation fairly easy and catalytic applications of this procedure are rather diffuse. In fact, the coordinated carbanion can undergo attack by an electrophile, which introduces the required functionality, as illustrated in the examples reported in Fig. 3.

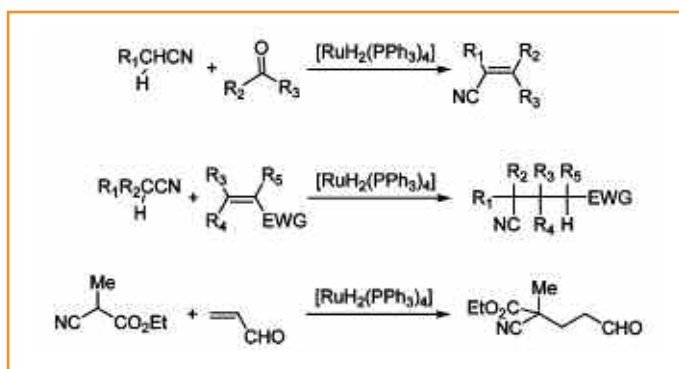
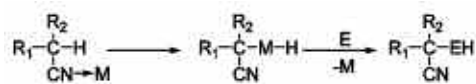


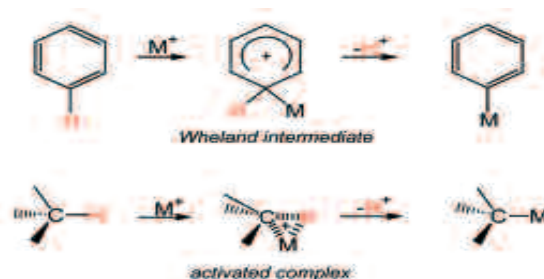
Fig. 3 - Intramolecular oxidative addition, favoured by the chelate effect: examples of catalytic applications



As a first general comment on the oxidative addition as a way to general and viable catalytic processes, it appears that intermolecular oxidative addition requires high energy “activated” complexes and this makes almost impossible the closure of any catalytic cycle. On the other hand the intramolecular oxidative addition is limited in scope, as it requires an additional electron withdrawing

group on the hydrocarbon skeleton, which helps C-H activation via chelate effects and increases the hydrogen acidity. So the short time perspectives appear rather problematic.

The situation is more promising with the TOA based on *Electrophilic Substitution*; this requires an electron poor metal centre, which behaves like a strong acid capable of replacing the proton in the C-H group. The first interaction with arenes is fairly easy as it affords the cationic Wheland intermediate, whereas with alkanes it gives a high energy activated complex:



The first historical example of this type of activation is the so called Shilov's reaction, in which a Pt(II) complex catalyzes the oxidation of CH_4 to CH_3OH ; the reaction is not very selective and unfortunately the oxidant is an expensive Pt(IV) complex. The potentiality of this approach has been fully exploited, to afford recently a synthetic application with the “Catalytica system”. This utilizes oleum as oxidant and reaction medium to give sulphuric acid methyl ester, which can be easily hydrolyzed to methanol. The catalyst is a Pt(II) complex and the mechanism is simplified as in Fig. 4 [10].

It should be underlined that the electrophilic activation step is favoured by the double positive charge on the complex.

The validity of this procedure for a selective oxidation of methane is confirmed by the results obtained by Herrmann's group on the synthesis of trifluoroacetate methyl ester from methane and trifluoroacetic acid, using potassium peroxodisulfate as oxidant and a

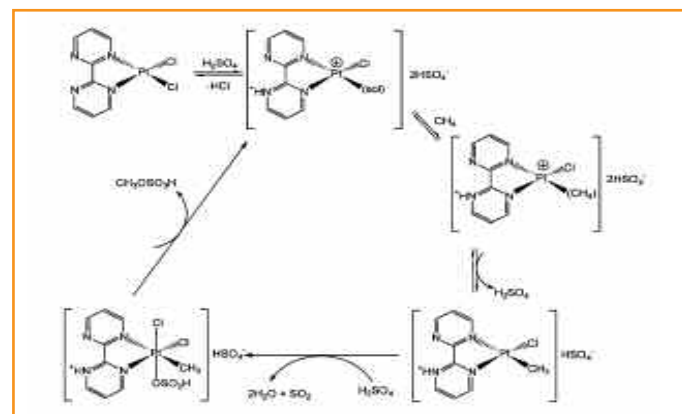
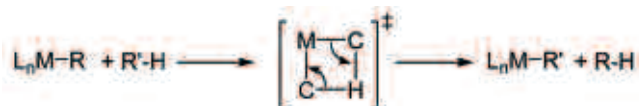


Fig. 4 - Simplified mechanism for “catalytica system”

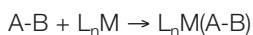
Pd(II) or Pt(II) dicarbene complex as catalyst [11].

It is probably not worthwhile to spend much words on the last TOA mechanism, *σ-Bond Metathesis*: it implies a transfer of a hydrogen atom from one ligand to another in a concerted fashion through a four centre, four electron transition state:



This way is similar to the electrophilic substitution, as, for example, the formal oxidation state of the metal centre remains constant. It is a well known process with organo metal substrates as lithium alkyls, Grignard reagents and recent examples involve also electron poor transition metal complexes as $Cp_2^*Lu-CH_3$.

Turning to the initial classification on the types of mechanism of C-H activation, the second one, *Metal-through-Ligand Activation*, MeLA, does not imply σ C-M bond and some authors define it as *C-H Functionalization*. The metal centre activates by coordination an organic moiety that subsequently reacts with the substrate causing C-H bond breaking:



A classical example is represented by the insertion of a metal-coordinated carbene fragment into a C-H bond, starting from a diazo derivative $N_2=C(R)R'$ [12]. In this case the driving force is the removal of N_2 released in the formation of the $M=C(R)R'$ reactive intermediate. This is clearly demonstrated by the data in Fig. 5, which show the beneficial effect of degassing the reacting solution on the efficiency of the process.

A contribution of our group is illustrated in Fig. 6, which shows how it is possible to functionalize the catalyst with fluorinated chains in

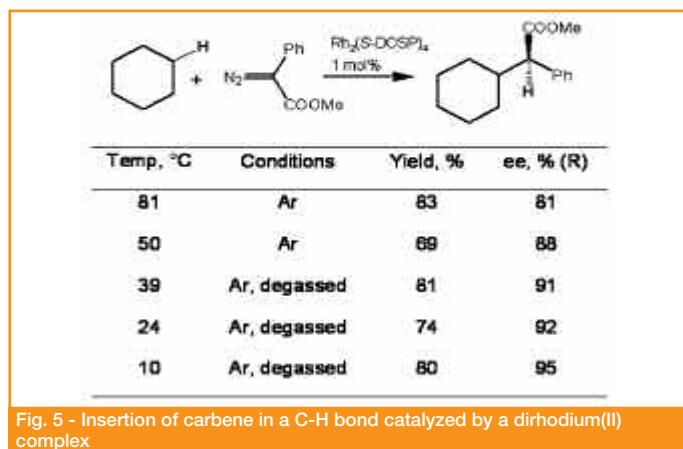


Fig. 5 - Insertion of carbene in a C-H bond catalyzed by a dirhodium(II) complex

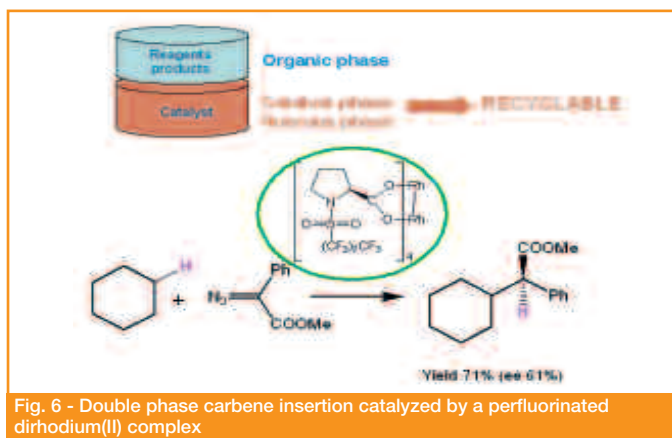
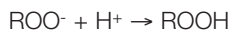
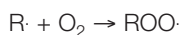
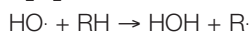


Fig. 6 - Double phase carbene insertion catalyzed by a perfluorinated dirhodium(II) complex

order to perform the same reaction in double phase in a more ambient friendly environment [13].

The obvious highest limitation of this procedure is the synthesis of the high energy reactive diazo derivatives.

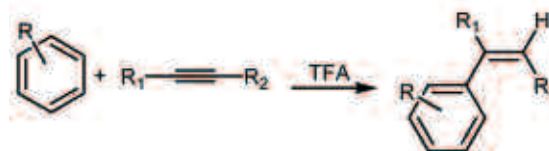
Very few words to comment the third type of C-H activation *Metal Initiated Activation*, MIA, where the role of the metal complex is simply that of generating an independent reactive species attacking C-H bond. In this case the best example is represented by the Fenton's reagent, in which the Fe complex is able to catalyse the oxidation of hydrocarbons with H_2O_2 or O_2 , through a reaction sequence of the type:



The mechanism is radical and as expected it suffers of limited selectivity.

Fujiwara's hydroarylation of alkynes: a case history

Passing to a discussion of a successful C-H activation, we will discuss the hydroarylation of alkynes. Fujiwara and coworkers were able to react a series of substituted arenes with alkynes, using palladium acetate as catalyst and a mixture of dichloromethane-trifluoroacetic acid as solvent [14]:



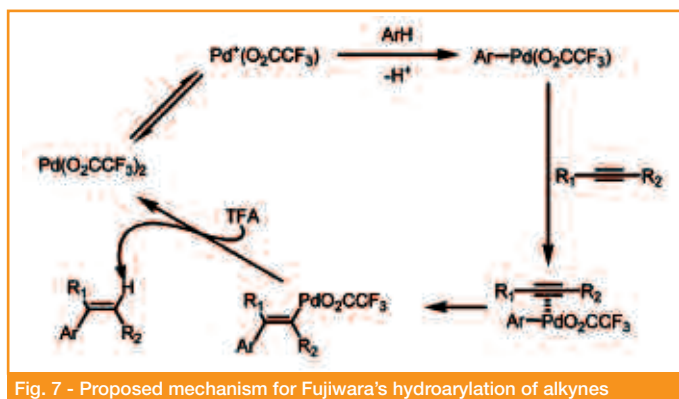


Fig. 7 - Proposed mechanism for Fujiwara's hydroarylation of alkynes

The mechanism proposed implies electrophilic C-H activation of the arene, followed by alkyne insertion, as described in Fig. 7.

This mechanistic proposal is in contrast with a subsequent study, which suggests a preliminary coordination/electrophilic activation of the alkyne [15], so that the attribution to a TOA or MeLA mechanism is not sure.

This reaction, however, is very interesting and we have tested as catalysts a series of dicarbene palladium complexes (Fig. 8), which have been already utilized as catalysts in Heck reaction [16]. This choice is based on their general very high stability even under acidic conditions [11]. Moreover monocarbene palladium(II) complexes are the only complexes which have been reported to be active in the Fujiwara reaction in the absence of other promoters, though their activity is only slightly superior to that of simple $\text{Pd}(\text{OAc})_2$ [17].

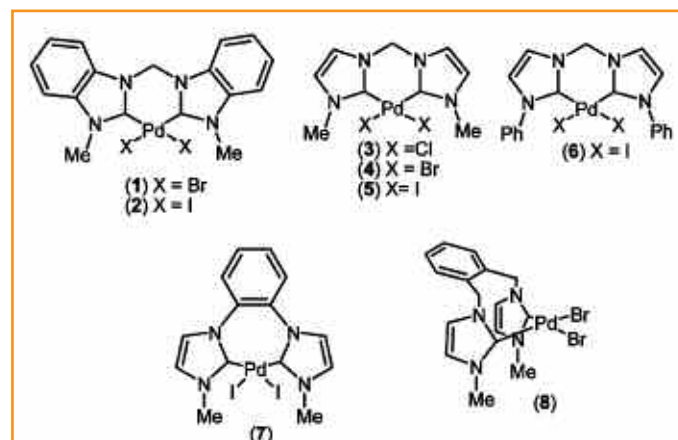


Fig. 8 - Palladium(II) dicarbene complexes tested as catalysts in Fujiwara's hydroarylation of alkynes

Preliminary tests indicate that our approach is very successful and the reaction occurs selectively with a very low catalyst content [18].

Conclusions

The final answer to the question on the title is obviously not so direct. C-H activation is not difficult, but catalytic synthetic applications surely require further deep studies on the scope of possible hydrocarbons, which can be functionalized, and on the type of metal centres to be utilized as catalysts. For this last aspect either a True Organometallic Activation (via electrophilic substitution) or a Metal-through-Ligand Activation seem more promising.

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Premi per Tesi di Laurea Specialistica in Discipline Chimiche

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Alla domanda di partecipazione dovrà essere allegata una breve presentazione dell'elaborato a firma del docente e un'eventuale nota da parte dell'impresa/associazione coinvolta. Dovrà anche essere allegata copia del Certificato di Laurea.

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