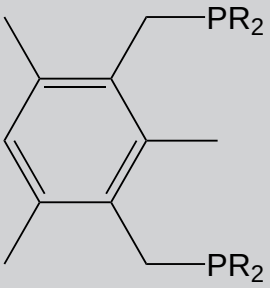
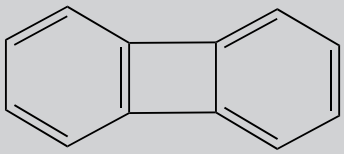


C-C



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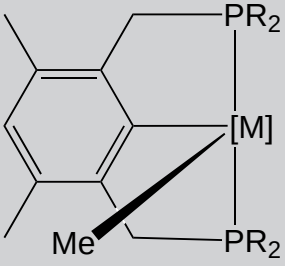
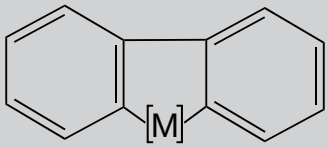


C-M-C



Transition metal insertion into C–C bonds in solution is a relatively unexplored reaction, particularly when strong C–C bonds are involved. The understanding of the reaction mechanisms, reactivity patterns, and factors controlling the competition between C–C and C–H activation may lead to the design of new selective processes for the utilization of hydrocarbons.

Metal Insertion into C–C Bonds in Solution

Boris Rybtchinski and David Milstein*

Dedicated to Professor Helmut Werner on the occasion of his 65th birthday

Metal-promoted activation of C–C bonds in homogeneous media under mild conditions may lead to the design of new selective processes for the utilization of hydrocarbons. However, examples of C–C bond activation in solution are much more scarce than those of C–H bond activation. We looked at the available data on metal insertion into C–C bonds in solution and tried to answer some important questions regarding the C–C bond activation. What kind of ligated metal center is necessary in order to cleave the "hidden" C–C bond? What are the possible mechanisms of the C–C activation in various reaction systems, and how do different metal centers influence the reactivity? How can one tune the metal center for C–C bond cleavage by varying the steric and electronic properties of ligands? Thermodynamically, insertion into a C–C bond in solution is not a forbidden process, even if no strain relief or aromatization driving force is involved. Moreover, with an appropriate system C–C activation may prevail thermodynamically and kinetically over the competing C–H activation. The relative thermodynamics of C–C versus C–H cleavage is influenced by the electron density on the metal center. When kinetics is concerned, coordinative unsaturation appears to be crucial for C–C oxidative addition.

Keywords: C–C activation · C–H activation · homogeneous catalysis

1. Introduction

Metal complex promoted activation of C–H and C–C bonds in homogeneous media is a field of much current interest since it can lead to the design of new selective and efficient processes for the utilization of hydrocarbons.[1] Beginning in the early 1960s, much effort has been invested in the field of C–H bond activation in solution. Landmarks involving metal insertion into C–H bonds include various cyclometalation processes,[2] intermolecular activation of aromatic C–H bonds,[1, 3] and insertion of a metal into C–H bonds of saturated hydrocarbons, including methane.[4] While C–H bond activation in solution is relatively well studied both synthetically and mechanistically, examples of C–C bond activation by soluble metal complexes are much less common, with the exception of strained C–C bonds (see Section 3).

There are several factors, mainly kinetic in nature, that favor C–H over C–C bond activation. These include 1) the generally easier approach of the metal center to C–H bonds, 2) the statistical abundance of C–H bonds, and 3) a substantially higher activation barrier for C–C versus C–H oxidative addition due to the more directed nature of the C–C bond (see Section 2). Nevertheless, in some cases these factors can be overcome. "Naked" metal atoms both in the gas phase and in matrices are capable of activating C–C bonds in alkanes (see Section 6). C–C activation in saturated hydrocarbons induced by superacids, such as $HSbF_6 \cdot SbF_5$, in solution is also known.[5] In this review we survey C–C bond activation processes in solution, confining ourselves to metal insertion into C–C single bonds. Alkene metathesis and β-alkyl elimination are beyond the scope of this review, as are C–C activations on surfaces and in the gas phase.

We believe that an understanding of the factors influencing metal insertion into C–C bonds and knowledge of the C–C bond activation mechanisms are key to the future development of this important field of organometallic chemistry. Therefore, in this review we pay special attention to studies which provide mechanistic insight regarding the C–C bond activation process.

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2. Thermodynamic and Kinetic Considerations

C–H bond activation is in general thermodynamically more favorable than C–C bond activation due to the fact that in

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solution, unlike in the gas phase (see Section 6), M–H bonds are generally considerably stronger than M–C bonds in alkyl metal complexes.[6] Nevertheless, C–C bond cleavage is not forbidden thermodynamically, as testified by several stable dialkyl metal complexes. Based on the known M–C bond strengths one can find systems in which metal insertion into a C–C bond will be not only thermodynamically feasible (i.e., BDE(M–C + M–C) > BDE(C–C); BDE = bond dissociation energy), but also more favorable than insertion into a C–H bond. For example, $M–C_{aryl}$ bonds are quite strong in the cases of rhodium and iridium, sometimes stronger than M–H bonds.[6, 7] Thus, substrates containing $C_{aryl}–R$ and $C_{aryl}–C_{aryl}$ bonds may be advantageous targets for iridium- or rhodium-mediated activation, although these bonds are stronger than $C_{sp^3}–C_{sp^3}$ bonds. However, the limited information regarding M–C bond strengths and the expected sensitivity of these bonds to steric effects interfere with the estimation of M–C bond energy in a specific metal complex, making the thermodynamic evaluations very rough. Energy gain from strain relief or aromatization appears to be a strong driving force for C–C cleavage (see Sections 3 and 4.2).

In cases where the C–C activation step is thermodynamically unfavorable, it may be accomplished by employing a subsequent "energy-releasing" step. For example, addition of H_2 may result in CH_4 elimination following the C–C activation step, making the overall process thermodynamically favorable even when very strong C–C bonds are involved.

The kinetic barrier is thought to be higher for C–C activation than for C–H activation. The common occurrence of stable polyalkyl metal complexes, in contrast to the rarity of alkyl metal hydrides, suggests that if thermodynamic factors favor reductive elimination, by microscopic reversibility arguments, there is a substantially higher kinetic barrier for C–C than for C–H activation. The "hidden" character of C–C bonds makes them kinetically much less attractive targets for activation by metals than the corresponding, more accessible, external C–H bonds. Still, although C–H activation is reversible in many systems, C–C oxidative addition is not generally observed.

The ease of approach of the active metal center to the bond to be cleaved is strongly influenced by the repulsive steric interaction of the ligands with the substrate. Thus, in the case of ligated metal complexes, C–C bonds are not only "chemically hidden" by C–H bonds, they are also sterically less accessible, unlike in the case of naked metals in a gas phase or matrices, or in the case of the naked proton of superacids.

Theoretical calculations point at another intrinsic problem in C–C activation.[8] With an implied three-centered nonpolar transition state, it was calculated that for first-row (3d) late transition metal atoms, the activation energies for insertion into the C–C bond of ethane and the C–H bond of methane are 40 – 45 and 20 – 25 kcal mol^{-1}, respectively. In the case of second-row (4d) late transition metals the barriers are substantially lower: 0 – 9 kcal mol^{-1} for C–H insertion and 13 – 27 kcal mol^{-1} for C–C insertion. The difference between the kinetic barriers for the C–C and C–H insertions is independent of the metal. This suggests that the insertion is largely influenced by the different nature of the C–C and C–H bonds and not by the nature of the metals. The key is the difference in orbital directionality between the C–H and C–C bonds. In the transition state leading to C–H oxidative addition the spherically symmetrical 1s orbital of the hydrogen atom can bind to the metal and carbon atom at the same time. The sp^3-hybridized carbon atom of the alkyl group has only one optimal binding direction, and in the course of C–H or C–C activation the alkyl groups have to rotate into a position that is no longer optimal for the R–H or R–R bond (Figure 1). Since in the case of C–C activation two alkyl groups are involved, the activation barrier for this process should be higher than that for C–H bonds, in which only one alkyl group participates.

3. Activation in Strained Systems

Metal-promoted C–C activation of strained alkanes has been known since the report by Chatt et al. in 1960,[9] in which the structure of a platinacyclobutane complex obtained by

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D. Milstein

B. Rybtchinski

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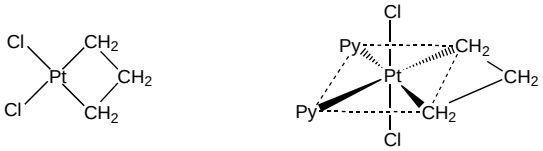
Figure 1. Schematic representation of R–H (left) and R–R bond cleavage (right) showing the influence of C–C and C–H orbital directionality on the oxidative addition process.

Tipper in 1955[10] as a product of cyclopropane oxidative addition was elucidated by NMR and IR studies of its bis(pyridine) derivative (Scheme 1). Since then a great deal of



Scheme 1. A platinacyclobutane complex (left) obtained by oxidative addition of cyclopropane and its bis(pyridine) derivative (right).

work on this topic has been published. The field has been reviewed by Bishop (on small ring rearrangements catalyzed by transition metals)[11] and by Jennings and Johnson (on the synthesis and properties of metalacyclobutanes).[12] Here we review only cases in which insertion of a transition metal into strained C–C bonds was clearly demonstrated and/or those that provide mechanistic insight regarding the C–C activation step.

Strain relief in the product and in the transition state provides an important thermodynamic and kinetic driving force for C–C activation in strained systems. The HOMO of cyclopropane and cyclobutane are largely p orbitals in character, forming "banana bonds" somewhat similar to the bonds in olefins (the same is true for the LUMO; it is similar to the π^* orbital of olefins). Thus, the symmetry and availability of the cyclopropane and cyclobutane HOMO and LUMO allow interaction with a metal HOMO (normally p_y) and LUMO (normally d_{xy}) in a way similar to a metal–olefin interaction. This lowers the kinetic barrier of the C–C cleavage reaction (Figure 2).

In an important early example, Cassar and Halpern demonstrated that $[\{Rh(CO)_2Cl\}_2]$ undergoes insertion into a strained C–C bond of quadricyclene by oxidative addition (Scheme 2).[13] In a similar way $[\{Rh(CO)_2Cl\}_2]$ oxidatively adds to the C–C bond of cubane.[14] In two other early reports, Ir[15] and Fe complexes[16] were demonstrated to insert into a C–C bond of cyclopropane to form structurally characterized oxidative addition metallacyclobutane products.

Various cyclopropanes react with Zeise's Pt^{II} dimer $[\{Pt(C_2H_4)Cl_2\}_2]$ to form tetrameric platina(IV)cyclobutanes, which upon addition of nitrogen donors provide the monomers in high yields, as was shown by McQuillin et al. (Scheme 3).[17]

Several reports refer to intermediacy of an "edge" platinum–cyclopropane complex, although such an intermediate has not been observed.[12] The existence of such a species en

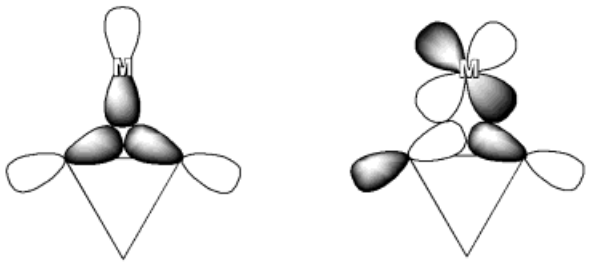
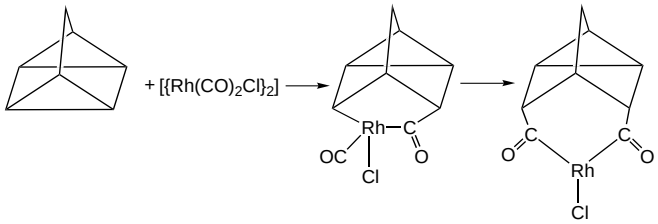
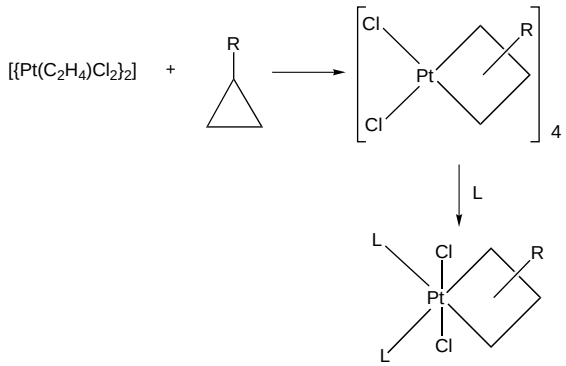


Figure 2. Cyclopropane–metal orbital interactions. Left: σ bond formed by the interaction of metal p_y and cyclopropane σ orbitals. Right: π bond formed by the interaction of metal d_{xy} and cyclopropane σ* orbitals.



Scheme 2. Reaction of quadricyclene with $[\{Rh(CO_2)Cl\}_2]$.



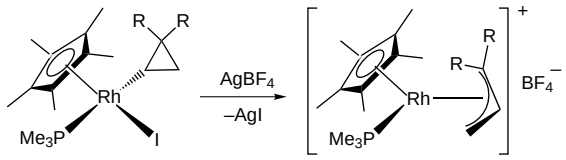
Scheme 3. Insertion of Pt^{II} into C–C bonds of cyclopropanes.

route to C–C activation seems reasonable for orbital symmetry reasons, since the banana bond is available for σ and π interaction with the HOMO and LUMO of the reactive metal center (Figure 2). Importantly, there is evidence that oxidative addition of cyclopropane to platinum occurs at an edge rather than at a corner of the ring.[12]

The oxidative addition of cyclopropanes to Zeise's dimer is limited in scope; with cyclopropanes bearing electron-withdrawing groups no direct platinacyclobutane formation is observed. This suggests that electrophilic attack of the Pt^{II} center on the cyclopropyl moiety is involved. On the other hand, Graziani et al.[18] and Ibers et al.[19] showed that Pt^0 and Pd^0 centers insert effectively into cyclopropanes substituted with electron-withdrawing groups, the low-valent metal center reacting as a nucleophile. Thus, as expected, the metal oxidation state strongly influences the affinity of a metal complex for various substrates, changing the mechanism of the reaction.

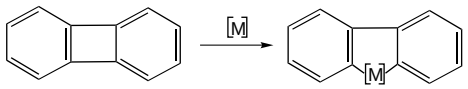
The mechanism of cyclopropane activation by the in situ generated [Cp*RhL] ($Cp^* = C_5Me_5$) fragment was studied in detail by Periana and Bergman.[20] Initially, C–H oxidative

addition takes place to yield the kinetic product [Cp*Rh(L)(cyclopropyl)(H)], which rearranges to rhodacyclobutane. The rearrangement was shown to be intramolecular (without alkane dissociation from the metal center) and regiospecific—the [Cp*RhL] moiety inserts only into the α C–C bond of the cyclopropyl ring. Steric constraints are important: In the case of substituted cyclopropanes insertion into the less substituted α C–C bond takes place. Importantly, when coordinative unsaturation was created by iodide abstraction with $AgBF_4$, a facile C–C cleavage reaction took place, resulting in formation of a π-allyl complex (Scheme 4).



Scheme 4. C–C bond activation in cyclopropane induced by iodide abstraction.

Metal insertion into the strained C–C bond of biphenylenes is another class of reactions which can be clearly identified as oxidative addition. This reaction is driven not only by strain relief but also by formation of two strong $M–C_{aryl}$ bonds (Scheme 5).



Scheme 5. Metal insertion into the strained C–C bond of biphenylene.

Eisch et al. showed that the reactivity of nickel complexes toward biphenylene increased in the sequence $[Ni(cod)(bpy)] < [Ni(Ph_3P)_4] < [Ni(C_2H_4)(Ph_3P)_2] < [Ni(Et_3P)_4]$ (cod = 1,5-cyclooctadiene, bpy = 2,2′-bipyrdiyl), demonstrating that higher electron density on the metal center promotes the C–C cleavage reaction, as expected for an oxidative addition process. Tetraphenylene derivatives were catalytically formed from biphenylene derivatives.[21]

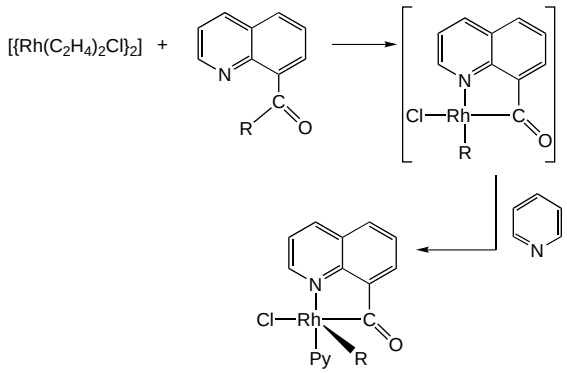
Jones et al. suggested that insertion of the $[Cp^*Rh(PMe_3)]$ fragment into the central ring of biphenylene proceeds intramolecularly via an η^2 coordinated species,[22] similarly to cyclopropane activation by this reactive metal fragment, as demonstrated by Periana and Bergman (see above).[20] $[Cp^*Rh(C_2H_4)_2]$ and $[Cp^*Co(C_2H_4)_2]$ were also shown to give C–C insertion products in the reaction with biphenylene.[23a] As reported by Jones et al., $[Pt(PEt_3)_2]$ and $[Pd(PEt_3)_2]$ insert into the biphenylene C–C bond to provide Pd^{II} and Pt^{II} complexes $[M(PEt_3)_2(2,2'\text{-biphenyl})]$, which are also capable of biphenylene C–C cleavage with prior phosphane dissociation. In this work C–C bond activation and formation result in a catalytic reaction to generate tetraphenylene.[23b] Insertion of Ir^I into the strained C–C bond of biphenylene was demonstrated by Crabtree et al.[24] Recently, Ito, Murakami et al. have demonstrated catalytic C–C cleavage of strained spirocyclobutanones with a Rh^I catalyst, $[Rh(cod)(dppe)]BF_4$ (dppe = 1,2-bis(diphenylphosphanyl)ethane).[25]

Even though a strong driving force for C–C activation is present in strained hydrocarbons, precoordination of the substrate is a necessity in most of the reported reaction systems. Recently it has been established that in many cases oxidative addition of an alkane C–H bond proceeds through precoordination of the alkane C–H bond to the metal.[1c] Taking into account the hidden and directed nature of the C–C bond, metal insertion into C–C bonds seems to be a kinetically (sterics and unfavorable orientation of the reactive orbitals) very demanding process, more so than that of the C–H bond.

4. Activation in Unstrained Systems

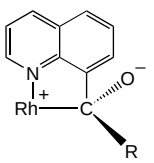
4.1. Activation of C–C Bonds Adjacent to a Carbonyl Group

Insertion of Rh^I into the α-keto C–C bond of 8-quinolinyl alkyl ketones takes place readily with $[\{Rh(C_2H_4)_2Cl\}_2]$, as demonstrated by Suggs et al. (Scheme 6).[26] The α-keto C–C bond is slightly weaker than other C–C single bonds, and, as



Scheme 6. Reaction of 8-quinolinyl alkyl ketones with $[\{Rh(C_2H_4)_2Cl\}_2]$.

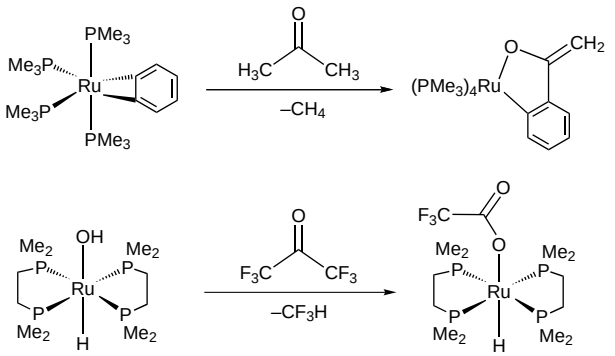
was pointed out by the authors, upon coordination to the nitrogen atom in the substrate the metal is somewhat directed at this bond, making the C–C activation both thermodynamically and kinetically feasible. Indeed, it was shown by labeling studies that direct C–C cleavage without prior C–H activation takes place.[26a] The carbonyl functionality not only weakens the C–C bond, but also plays an important role in the C–C cleavage process: Chiral induction at the Rh center suggests that a tetrahedral intermediate (Scheme 7) is on the path to



Scheme 7. Tetrahedral intermediate proposed for cleavage of the C–C bond in 8-quinolinyl alkyl ketones.

C–C cleavage in 8-quinolinyl alkyl ketones. Thus, the reaction mechanism is similar to that of the Baeyer–Villiger reduction of ketones.[26c]

Bergman et al. demonstrated that ruthenium complexes capable of producing unsaturated species cleave the C–C bond in acetone[27] and hexafluoroacetone[28] (Scheme 8).

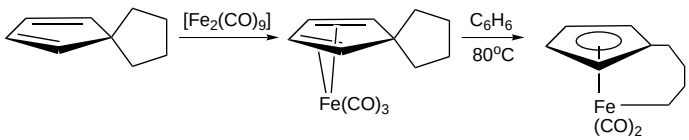


Scheme 8. Ruthenium-promoted cleavage of the C–C bond in acetone and hexafluoroacetone.

Cleavage of the C–C bond in cyclic aliphatic ketones with $[Rh(PPh_3)_3Cl]$ has been reported by Murakami, Ito et al. Exclusive activation of the less substituted C–C bond α to a carbonyl group has been observed. Catalytic C–C bond activation in cyclic ketones using hydrogen has been also demonstrated.[29]

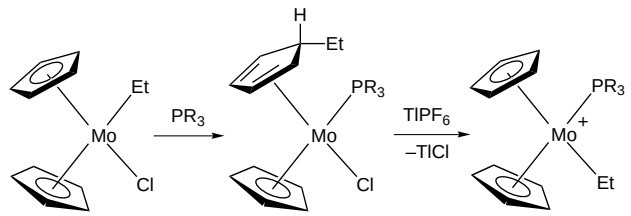
4.2. Activation of C–C Bonds Driven by Aromatization

Eilbracht et al. showed that C–C single bonds within tricarbonyliron complexes of 1,1-dialkyl-substituted spiro cyclopentadienes were cleaved in boiling benzene, leading to π-cyclopentadienyl-σ-alkylcarbonyliron complexes.[30] Crossover experiments demonstrated that the *endo*-alkyl group is intramolecularly transferred from the diene ligand to the metal (Scheme 9).



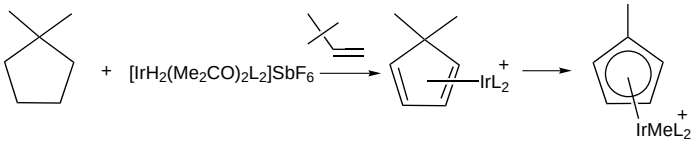
Scheme 9. Cleavage of C–C bonds in tricarbonyliron complexes of 1,1-dialkyl-substituted spiro cyclopentadienes.

Green et al. reported a similar molybdenum system in which a reversible metal-to-ring transfer of an ethyl group occurs when a free coordination site on the metal center is generated by chloride abstraction (Scheme 10).[31]



Scheme 10. C–C bond activation by a reversible metal-to-ring transfer of an ethyl group. $PR_3 = PEt_3$, PMe_2Ph, $PMePh_2$.

Crabtree et al. reported C–C bond cleavage in cationic 1,1-dialkyl-substituted cyclopentadienyliridium complexes. An elegant two-step route with prior dehydrogenation of the alkane was developed, leading to an overall selective C–C bond breaking in disubstituted cyclopentanes (Scheme 11).[32] Interestingly, no C–C cleavage was observed with the analogous saturated 18e complex, containing a dialkylcyclohexadienyl ligand, under various reaction conditions. Thus, coordinative unsaturation was suggested to play a key role in the process of C–C activation.[32b]



Scheme 11. C–C bond cleavage in cationic 1,1-dialkyl-substituted cyclopentadienyliridium complexes. $L = P(p\text{-}FC_6H_4)_3$.

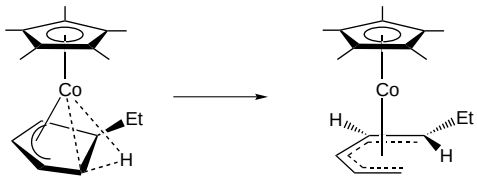
The energy gain from aromatization in the systems described above renders the processes thermodynamically feasible. The orientation of the alkyl group towards the metal center in the rigidly coordinated cyclopentadiene is favorable for C–C cleavage, making the process also kinetically feasible. The *endo*-alkyl group which is closer to the metal center is always the one transferred to the metal.

Maitlis et al. described an unusual rhodium-assisted C–C cleavage in Dewar benzene to produce a cyclopentadienylrhodium dimer.[33] The driving force for the overall process is clearly aromatization to form two Cp rings. Palladium-promoted isomerization of Dewar benzene into hexamethylbenzene was also observed, aromatization being a strong driving force for this reaction.[34]

Chaudret et al. demonstrated that reaction of the electrophilic fragment $[Cp^*Ru]^+$ with the A rings of steroids resulted in aromatization through cleavage of various bonds, including C–C bonds.[35] A driving force for these reactions is the remarkably high affinity of the cationic ruthenium fragment for aromatic hydrocarbons. Significantly, the aromatization occurs when the ruthenium moiety and the methyl group being activated are located on opposite faces of the steroid substrate. Based on this, and on the observation of ethane in the gas phase of the reaction mixture, presumably formed by coupling of two methyl radicals, it was suggested by the authors that the C–C cleavage process proceeds by a radical mechanism.

4.3. C–C Bond Cleavage in Unsaturated Cobalt Complexes Stabilized by an Agostic Interaction

Bennett and Spencer et al. have demonstrated an interesting case of C–C cleavage in unsaturated cationic cobalt complexes stabilized by an agostic interaction[36] (Scheme 12).



Scheme 12. C–C cleavage in unsaturated cationic cobalt complexes stabilized by an agostic interaction.

In these complexes the diene-hydride form is of higher energy than the species stabilized by the agostic interaction with the C–H bond. Thus, the product of C–H activation is not stable, making C–C activation thermodynamically more favorable. A thermodynamic driving force such as relief of strain by opening of a cyclic five-membered allyl is present. No C–C cleavage was observed in six-membered rings either due to thermodynamic factors (stability of six-membered rings) or kinetic factors (poor accessibility of C–C bonds to the metal), as suggested by the authors.

4.4. C–C Activation Involving More than One Metal Center

Cluster-promoted scission of a coordinated alkyne in solution providing alkylidene fragments was demonstrated with a variety of metal carbonyl clusters. Alkyne migration to the edge of the cluster is required, and subsequent CO loss triggers the C–C bond cleavage. Coordinative unsaturation appears to be a prerequisite for the reaction.[37]

C–C bonds of cumulenes and diynes were also successfully cleaved in carbonyl clusters or in bimetallic complexes. The C–C bonds in these compounds are more accessible due to the absence of C–H bonds.[38]

An interesting example of selective C–C bond cleavage in cyclopentadiene by an unsaturated trinuclear ruthenium cluster has been reported by Suzuki et al. It was suggested that the three metal centers cooperate in the activation.[39]

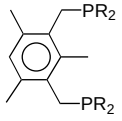
Recently Johnson et al. have shown that the trinuclear cluster $[Ru_3(CO)_{12}]$ is capable of activating C–C bonds in cyclohexene and cycloocta-1,3-diene upon heating under reflux in octane.[40] However, the product of C–C activation was obtained in low yield.

4.5. Electrochemically Induced Oxidative Addition of C–C Bonds

As shown by Geiger et al., electrochemical oxidation of the pseudo-triple-decker complex $[Cp_2Ru_2(\mu\text{-}cyclo\text{-}C_8H_8)]$ results in the flyover dication $[Cp_2Ru_2(\mu\text{-}cat\text{-}C_8H_8)]^{2+}$, in which the C_8H_8 group is an open chain. Thus, the redox process induces insertion of both metal atoms into a C–C bond of cyclooctatetraene.[41] The C–C bond being cleaved bridges the two Ru centers in $[Cp_2Ru_2(\mu\text{-}cyclo\text{-}C_8H_8)]$. As a consequence it is fairly long (1.570(6) Å) and can be defined as "preactivated". The orientation of the bond is ideal for C–C cleavage, since only electron redistribution is needed for the C–C rupture, which is induced by an electrochemical two-electron oxidation.

4.6. Metal Insertion into an Unstrained C–C Bond in PCP and PCN Systems

As discussed above, most of the examples of C–C bond activation by insertion of soluble metal complexes include a drive to aromatic character in prearomatic systems, the presence of a carbonyl group, or strain. When we set the goal of studying the activation of strong, unstrained C–C bonds, we chose an intramolecular process in order to bring a metal center close to the "hidden" C–C bonds. For an unequivocal demonstration and mechanistic evaluation of metal insertion into a C–C bond, it is desirable that this process would be irreversible, and that the C–C activation product would be stable and readily characterized. The substrates of our choice, PCP ligands (Scheme 13), possess the required properties. They can be viewed as a mesitylene molecule with two attached phosphane "arms". The C_{Me}–C_{aryl} bonds of these ligands, targeted for metal insertion, are very strong (e.g. $BDE(C_6H_5\text{–}CH_3) = 101.8 \pm 2\ kcal\,mol^{-1}$), stronger than the competing benzylic C–H bonds (e.g. $BDE(C_6H_5CH_2\text{–}H) = 88 \pm 1\ kcal\,mol^{-1}$).[42] The presence of two types of C_{Me}–C_{aryl} bonds which are potentially available for C–C activation in these systems can provide additional information regarding this process.



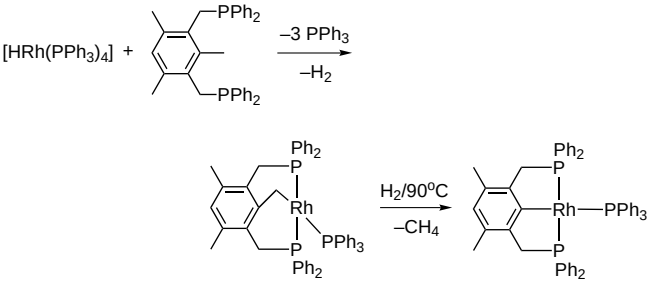
Scheme 13. Schematic representation of the PCP ligands.

The process of C–C activation in a PCP ligand can be viewed as being similar to the well-known cyclometalation of the C–H bond situated between the phosphane arms. The expected competing reaction, metal insertion into the benzylic C–H bond of a PCP ligand, may be reversible and would allow a comparison between the two processes.

4.6.1. Insertion into a Strong C–C Bond in Solution: C–C versus C–H Activation

4.6.1.1. C–C Activation—Demonstration of the Process

The first example of metal insertion into an unstrained, unactivated C–C bond in solution was demonstrated with $[HRh(PPh_3)_4]$.[43] The use of a metal hydride complex was intended to provide a substantial driving force to the overall C–C activation process by the expected methane elimination following insertion into the C–C bond. Reaction of $[HRh(PPh_3)_4]$ with the Ph-PCP ligand at room temperature resulted in elimination of H_2 and formation of the kinetic C–H activation product (Scheme 14). Significantly, the C–H activation process can be reversed by heating of this product under a mild hydrogen pressure, resulting in quantitative C–C cleavage and methane elimination.



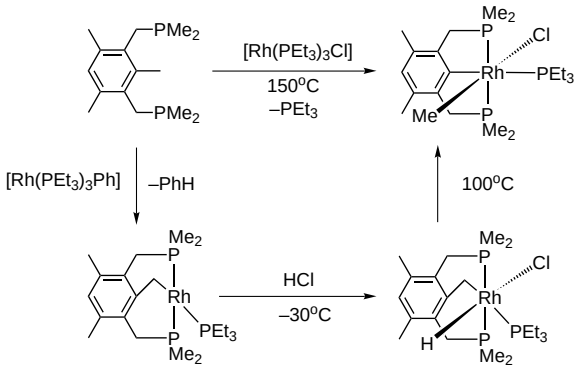
Scheme 14. Reaction of $[HRh(PPh_3)_4]$ with Ph-PCP.

As the complex with the the activated C–C bond does not react with methane, the overall C–C activation process is irreversible and thermodynamically more favorable than the overall C–H activation sequence. The use of hydrogen to drive the reaction towards C–C activation could potentially

be utilized as a general strategy to overcome the problem of C–H activation which is expected to accompany C–C activation in hydrocarbons. While the intimate mechanism of C–C activation was unclear at that stage, a three–centered transition state and/or an η^2-arene intermediate were suggested to be on the reaction pathway.

4.6.1.2. C–C versus C–H Activation—Thermodynamics

Employment of hydrogen in the above-mentioned process masks the relative thermodynamic stability of the C–H and C–C activation products, leaving open the questions of the thermodynamic feasibility of the oxidative addition of a strong C–C bond in the absence of added reagents and the thermodynamic interplay between C–C and C–H oxidative addition. Direct C–C insertion in the absence of hydrogen proved to be thermodynamically feasible with Me-PCP. Heating this ligand with $[Rh(PEt_3)_3Cl]$ led to the product of direct C–C activation quantitatively (Scheme 15, Figure 3).[44]



Scheme 15. Insertion of Rh into C–C and C–H bonds of the Me-PCP ligand.

The C–H activation product, which was prepared by an independent route, is quantitatively converted into the C–C activation product upon heating (Scheme 15), unambiguously proving that Rh^I insertion into the C–C bond in this system is thermodynamically more favorable than insertion into the C–H bond.

The C_{Me}–C_{aryl} bond in PCP ligands is much stronger than the (aryl)CH_2–H (C_{benzyl}–H) bond ($BDE(C_6H_5–CH_3) = 101.8 \pm 2$ versus $BDE(C_6H_5CH_2–H) = 88 \pm 1$ kcal mol^{-1} [42]), indicating that conversion of the C–H activation product into the C–C activation product is product-controlled and that $BDE(Rh–C_{aryl} + Rh–CH_3) > BDE(Rh–CH_2(aryl) + Rh–H)$. This is in accord with the observation that the strongest bonds to metals are usually formed by breaking of the strongest bonds in the substrates.[7, 45] Formation of the strong Rh–C_{aryl} bond most probably is a driving force for the reaction (see above). The expected slightly lower stability of the six-membered chelate ring in the C–H activation complexes, as compared to the five-membered ring in the C–C activation complexes, may also influence their relative stability. Importantly, decreasing the electron density on the metal, when Ph instead of Me substituents are attached to a phosphane, results in stabilizing the product of C–H activation, which does not undergo C–C activation even upon heating to 150°.[44]

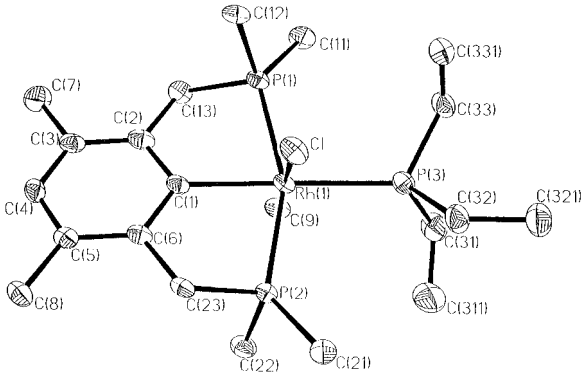
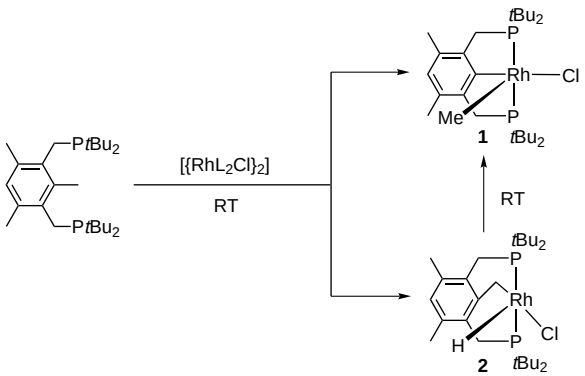


Figure 3. ORTEP diagram of the C–C activation complex [Cl(Me-PCP)Rh(CH_3)(PEt_3)] (see Scheme 15). Hydrogen atoms are omitted for clarity.

4.6.1.3. C–C versus C–H Activation—Mechanism

After it was demonstrated that Rh^I insertion into the C–C bond in the PCP systems is thermodynamically feasible and can be preferable to insertion into the C–H bond, the question of the reaction mechanism was addressed. Is the mechanism polar or nonpolar? What is the role of the aromatic ring in the process? Is it a direct process or does it require prior C–H activation followed by some rearrangement to the C–C activation product? Mechanistic studies were performed on the reaction of the bulky *t*Bu-PCP ligands with Rh^I and Ir^I.

Bulky phosphanes are advantageous ligands for the study of oxidative addition processes, especially cyclometalations, since upon coordination to a metal center they generate a species having a shielded vacant coordination site and a congested conformation. The latter assists the cyclometalation process due to favorable entropy.[2a] Remarkably, when the *t*Bu-PCP ligand was allowed to react with rhodium olefin dimers at *room temperature*, direct rhodium insertion into one of the strong aryl–carbon bonds took place, yielding the product of C–C oxidative addition **1**, the structure of which was elucidated by X-ray analysis (Scheme 16).[46a] At the beginning of the reaction the product of C–C oxidative addition was formed concurrently with the product of C–H oxidative addition, the latter being converted into the former

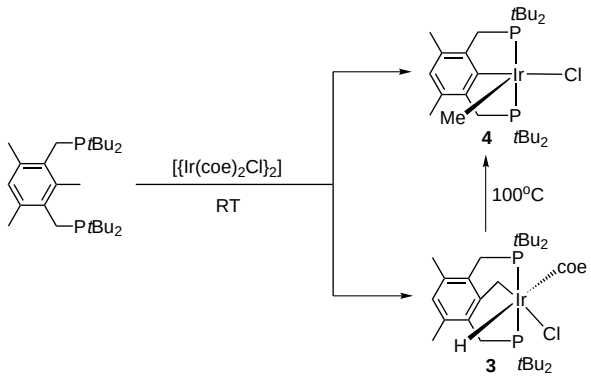


Scheme 16. Reaction of *t*Bu-PCP with $[\{RhL_2Cl\}_2]$. L = cyclooctene, ethylene, *tert*-butylethylene.

within several hours. These observations indicate that the "methylene bridged" compound **2** undergoes slow C–H reductive elimination, followed by rapid metal insertion into the C–C bond.

Increasing the steric bulk of the alkene ligand in the $[\{RhL_2Cl\}_2]$ complex resulted in a large decrease in the overall reaction rate. The reaction is very fast with the ethylene complex and slow with the *tert*-butylethylene one. This reactivity order indicates that associative displacement of the alkene by the phosphane takes place and that the initial coordination of the diphosphane ligand to the rhodium olefin complex is the rate-determining step for the entire process rather than the C–C or C–H activation steps. Nevertheless, important mechanistic conclusions could be obtained from a comparison of these steps (see below).

Concurrent formation of the C–H and C–C activation products took place in the reaction of $[\{Ir(coe)_2Cl\}_2]$ (coe = cyclooctene) with the *t*Bu-PCP ligand at room temperature. The product of C–H activation, complex **3**, is quantitatively converted into the C–C activation product, complex **4**, upon moderate heating (Scheme 17).[46a] However, in contrast with the rhodium complex **2**, **3** is stable under the reaction conditions, making the study of the process easier.



Scheme 17. Reaction of *t*Bu-PCP with $[\{Ir(coe)_2Cl\}_2]$.

The above-mentioned reactivity unequivocally proves that the insertion of iridium and rhodium into the C–C bond is thermodynamically more favorable than insertion into the C–H bond, as observed in the Me-PCP system (see above). In the case of iridium the ratio between the products of C–C and C–H activation was constant at different temperatures during the course of the reaction and remained the same after the reaction was complete (C–H:C–C is 1.75 ± 0.07 in benzene and 2.29 ± 0.08 in THF, Scheme 17). The C–H and C–C insertion products were formed irreversibly within the temperature range of 20–60 °C, indicating that the C–C and C–H activation processes are kinetically controlled; the constant ratio demonstrates that the complexes are formed in two independent, concurrent processes. Thus, the C–H activation product **3** is not an intermediate in the C–C activation process, as verified by the observation that it does not convert into the C–C activation product under the reaction conditions. Both the C–C and C–H activation processes were shown to proceed through a common intermediate with the two phosphane arms coordinated to the metal center. Thus, taking into account that the product ratio is temperature-independent and that three C–H bonds per one C–C bond are accessible for activation, $\Delta\Delta H^{\neq}_{CH-CC} \approx 0$ kcal mol^{-1} and $\Delta\Delta S^{\neq}_{CH-CC} = -1.07 \pm 0.05$ eu. Surprisingly, the kinetic barrier for C–C oxidative addition is slightly lower than that for C–H ($\Delta\Delta G^{\neq}_{CH-CC}$ (293) = 0.342 kcal mol^{-1}, Figure 4).

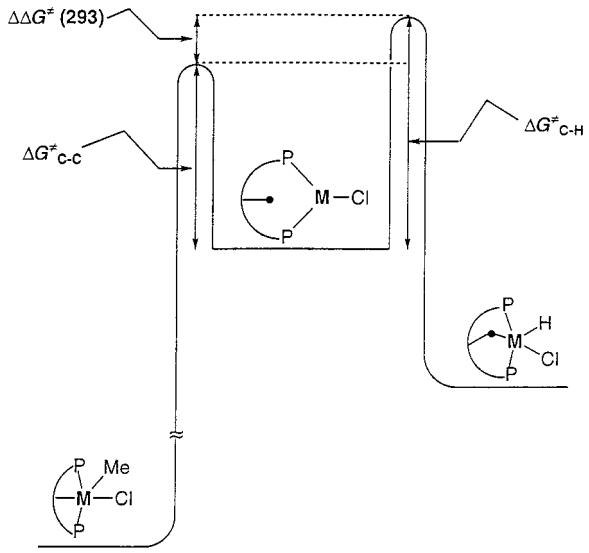


Figure 4. Reaction profile for C–C versus C–H oxidative addition. $\Delta\Delta G^{\neq}(293) = 0.3$ (M = Ir), 0.5 kcal mol^{-1} (M = Rh).

The mechanistic aspects of C–H bond activation by low-valent late transition metals were extensively studied. It was shown that C–H bond breaking involves an early three-centered, nonpolar transition state.[1] The striking similarity of the activation parameters for C–C and C–H activation processes, and the fact that the activation parameters are not much affected by variation in solvent polarity (benzene and THF) or by the use of a *para*-methoxy-[46a] and *para*-carboxy-substituted derivatives[46b] of the *t*Bu-PCP ligand, indicates that similar nonpolar transition states are involved in both processes. The lack of substituent effect also suggests that a η^2-arene complex is not involved in the C–C activation process. The η^2-arene complex is generally thought to be an intermediate which brings the metal into the proximity of the C–H[3a] or C–C bond[22] to be cleaved. Taking into account that in the metal–PCP system the metal center is already held in the vicinity of the C–C bond by coordination to the two phosphane moieties, precoordination of the aromatic ring does not seem to be required in the reaction course. Thus, oxidative addition of the C–C bond in our system most probably proceeds through a three-center, nonpolar transition state similar to that postulated for aliphatic C–H bond activation.

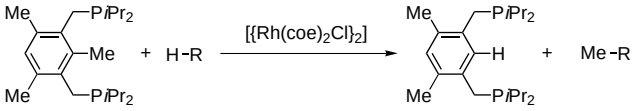
The observed similarity in the kinetic barriers for the C–H and C–C activation processes is in striking contradiction with the common belief that the barrier for C–C activation is much higher than that of C–H activation. Theoretical calculations predict that due to the difference in directionality between bonds to methyl groups and to the hydrogen atom, the activation energy of oxidative addition of the C–C bond

should be substantially higher (by about 10 – 20 kcal mol^{-1}) than that of the C–H bond (see Section 2). The surprising kinetic preference for the C–C bond activation in our system can be accounted for in terms of the specific directionality of the reactive metal orbitals towards the C–C and C–H bonds, favoring the oxidative addition of the former.

It is remarkable that direct insertion into a very strong C–C bond in solution can take place even at room temperature. Moreover, the insertion is not the rate-determining step. This can be attributed to factors favoring oxidative addition in the *t*Bu-PCP system. The two *tert*-butylphosphane groups bring the metal into the vicinity of the C–C bond to be activated and enhance the electron density on the metal center, while the bulky *tert*-butyl substituents are capable of shielding a vacant coordination site and imposing a conformation that favors cyclometalation.[2a] Unsaturation in the reactive intermediate seems to be very important, since heating to 150 °C was required in order to achieve C–C oxidative addition with Me-PCP (see above). This may be a result of the much lower steric bulk of the methylphosphane ligands, which permits the formation of a four-coordinate Rh^{I} complex prior to the C–C activation process.

4.6.1.4. Catalytic C–C Activation

An unstrained, strong C_{aryl}–C bond can be catalytically cleaved by a metal complex in solution. In this unprecedented transformation, reaction of [{Rh(coe)$_2$Cl}$_2$] with an excess of 1,3-bis(diisopropylphosphanylmethyl)mesitylene in dioxane under a mild H_2 pressure or with an excess of HSi(OEt)$_3$ results in catalytic, selective cleavage of one of the C–C bonds in the diphosphane (Scheme 18). Although the catalytic



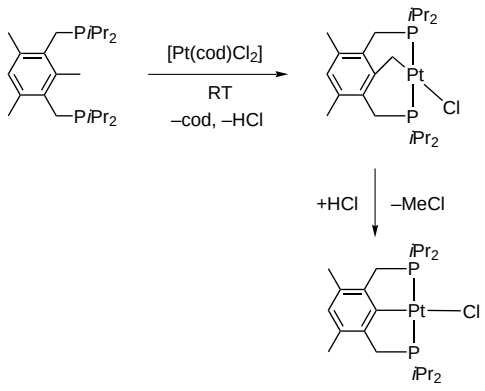
Scheme 18. Reaction of *i*Pr-PCP with H–R (R = H, Si(OEt)$_3$).

reactions were not optimized, more than 100 turnovers were observed in the case of H_2. A mechanistic scheme has been proposed.[47]

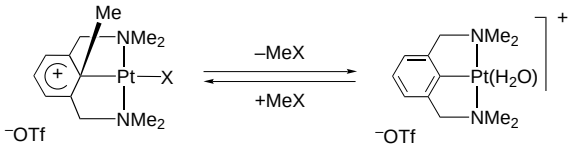
4.6.1.5. C–C versus C–H Activation by Pt

The C–C bond in PCP ligands was also cleaved by Pt^{II} (Scheme 19).[48] The kinetic C–H activation product was quantitatively converted into the C–C activation product by addition of HCl. Pt^{II} is known to activate C–H bonds both by electrophilic and nucleophilic mechanisms.[2b] C–C activation in the PCP system can proceed by an electrophilic attack on the aromatic ring with a subsequent 1,2-methyl shift from the coordinated alkyl group to Pt in an arenium cation intermediate.

Importantly, in the closely related NCN system such a 1,2-methyl shift is a plausible mechanistic step, as shown in the work of van Koten et al.[49] A Pt-NCN arenium complex was demonstrated to promote reversible C–C bond formation and activation (Scheme 20). C–C bond activation in this system appears to be driven by aromatization (see Section 4.2)



Scheme 19. Cleavage of the C–C bond in *i*Pr-PCP by Pt^{II}.

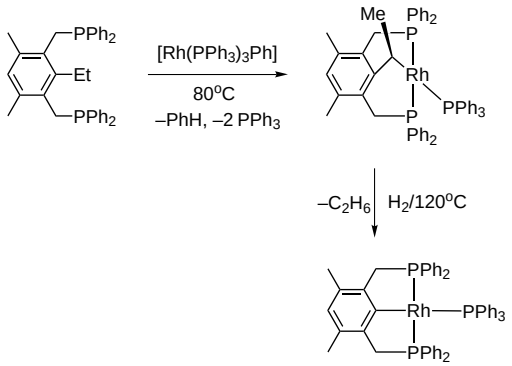


Scheme 20. Reversible C–C bond activation in a Pt-NCN arenium complex. X = Cl, Br, I; OTf = trifluoromethansulfonate.

4.6.1.6. C_{aryl}–CF_3 and C_{aryl}–Et Activation: C–C versus C–F and C_{sp^3}–C_{sp^3} versus C_{sp^3}–C_{sp^2}

When the CH_3 group between the phosphane arms of the *t*Bu-PCP ligand is changed for CF_3, selective oxidative addition of the very strong C_{aryl}–CF_3 bond takes place in the reaction with [{RhL$_2$Cl}$_2$] (L = ethylene, cyclooctene). No (aryl)CF_2–F activation product was observed.[50] Both nonpolar and polar (nucleophilic attack) mechanisms are possible, and further studies are required.

The possibility of competitive activation of C_{sp^3}–C_{sp^3} versus C_{sp^3}–C_{sp^2} bonds was studied with a PCP ligand containing an aryl-Et moiety. Upon reaction with Rh^{I} complexes, oxidative addition of C–H initially takes place. Heating of the C–H activation product at 120 °C under H_2 results in selective C_{sp^3}–C_{sp^2} cleavage, yielding the C–C activation product and ethane (no methane was detected, Scheme 21).[51] Direct



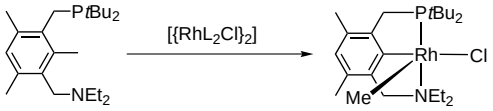
Scheme 21. Reaction of a PCP ligand containing an aryl-Et moiety with [Rh(PPh$_3$)$_3$Ph].

C_{sp^3}–C_{sp^2} bond activation in *t*Bu-PCP ligand containing an aryl-Et moiety was also observed.[51b] Significantly, a pathway, involving consecutive C_{sp^3}–C_{sp^3} and C_{sp^3}–C_{sp^2} bond cleavages, generating methane and the same C–C activation complex

would have been thermodynamically much more favorable (by about 28 kcal mol^{-1}) than the observed C_{sp^3}–C_{sp^2} cleavage. The reason for the exclusive ethane formation is clearly kinetic. We believe that the specific orientation of the reactive metal orbitals is responsible for the observed preference.

4.6.1.7. The PCN System

A unique preference for C–C activation has been recently demonstrated in the new PCN system.[52] Upon reaction of a PCN ligand with $[\{RhL_2Cl\}_2]$ (L = ethylene, cyclooctene) at room temperature or below, exclusive C–C activation took place and no C–H activation products were observed (Scheme 22). This may be due to the sterically less crowded metal center in the reactive intermediate ($PtBu_2$ is bulkier than NEt_2; compare the cone angles of $EtPtBu_2$ (162°) versus NEt_3 (150°)). The electronic influence of replacing the soft phosphane ligand by a hard amine may



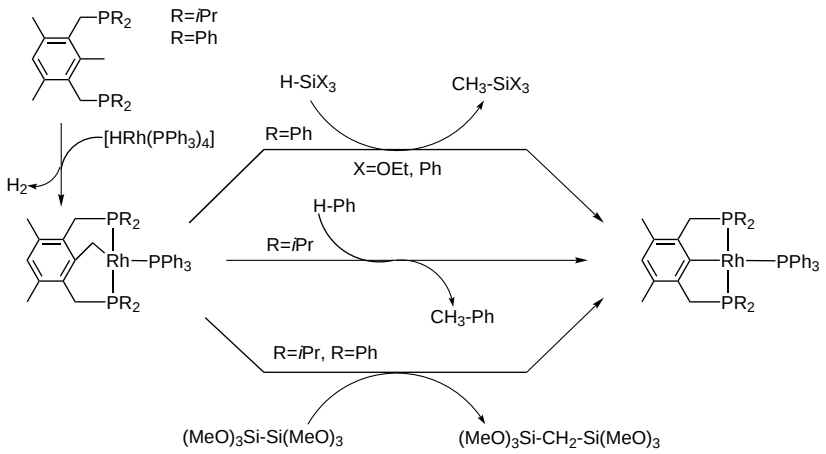
Scheme 22. Reaction of a PCN ligand with $[\{RhL_2Cl\}_2]$. L = ethylene, cyclooctene.

also influence the reactivity of the metal center in the C–C versus C–H oxidative addition. The possibility of a rapid, reversible C–H activation process involving a short-lived (on the NMR time scale), unobserved, C–H activated complex cannot be discounted. A likely reason for fast C–H reductive elimination in this system (in comparison to the PCP system) may be a rapid, reversible on–off dissociation of the amine arm.

In the first example of metal insertion into an unstrained, unactivated C–C bond in solution, we used hydrogen and heating to suppress C–H activation. Then we demonstrated that direct C–C activation can be achieved at elevated temperatures and at room temperature or lower with concurrent C–H activation. In the case of the PCN ligand system direct C–C insertion takes place even at −30 °C, with no formation of C–H activation product. This ligand seems to be perfectly designed for C–C cleavage.

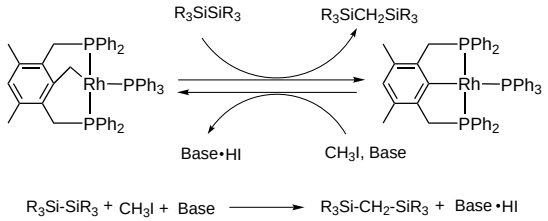
4.6.2. The Methylene Transfer Reaction

The ability to insert a metal into an unactivated C–C bond raises the possibility that a hydrocarbon could serve as a source of methylene groups. If the inserted metal center is capable of binding and activating an additional substrate, the result could be selective insertion of the methylene group into another chemical bond. Indeed, the methylene group in the "methylene-bridged" complexes can be abstracted not only by H_2 but by a variety of reagents. The methylene group was inserted into Si–H, Si–Si, and C_{aryl}–H bonds (Scheme 23).[53] This represents a conceptually new process in organometallic



Scheme 23. Insertion of a methylene group into Si–H, Si–Si, and C_{aryl}–H bonds.

chemistry and an unusual combination of reactions: C–C bond cleavage, methylene transfer, and selective incorporation into other bonds. Interestingly, the methylene group can be regenerated by treatment of complex whose C–C bond was cleaved with methyl iodide and a base. In this two-step process a methylene group is extruded from MeI and selectively incorporated into a Si–Si bond (Scheme 24). A mechanism



Scheme 24. Regeneration of the methylene group. The overall reaction is given at the bottom.

accounting for the methylene group transfer may include oxidative addition of the substrate with subsequent C–C bond cleavage by a three-coordinate Rh^I fragment and, finally, product release by reductive elimination.

Remarkably, in a one-pot reaction it was possible to combine selective C–C cleavage with the activation of other strong bonds to form products of methylene group transfer. As expected, the electron density on the metal center is an important tool in adjusting the reactivity towards various substrates. Thus, hydrosilylation of a C–C bond was demonstrated with a complex containing phenylphosphane moieties. In the case of methylene group insertion into benzene, a higher electron density on the metal is needed in order to oxidatively add the less reactive C–H bond, and, hence, a complex with isopropylphosphane moieties was used. The reactivity of the Si–Si bond is intermediate to that of Si–H and C–H; therefore both phenyl- and isopropylphosphane complexes transfer the methylene group to the disilane.

4.6.3. C–C versus C–H Activation: Substituent Effects

There is a remarkable influence of the phosphane substituents of PCP ligands on the thermodynamics and kinetics of C–C and C–H activation. Tuning the electron density and

sterics on the metal center by choice of different substituents in the PCP ligands or use of the PCN ligand made possible regulation of the reaction preferences, and selective C–C or C–H activation was achieved.

Thus, Me-PCP, *i*Pr-PCP, and *t*Bu-PCP ligands result in more stable C–C insertion products (Section 4.6.1), whereas the less basic Ph-PCP thermodynamically favors C–H activation (Section 4.6.1.2). This demonstrates the importance of electron density on the metal center in the thermodynamic balance between C–C and C–H oxidative addition (Table 1). Steric factors are apparently of minor importance here, taking into consideration the wide variation in the alkylphosphane size. When higher electron density is involved, metal insertion into the C_{aryl}–CH_3 bond becomes thermodynamically more favorable than insertion into the (aryl)CH_2–H bond. This is perhaps due to the possibility of backbonding from the metal in C_{aryl}–M into the aryl π^* system, which stabilizes the C_{aryl}–M bond relative to the (aryl)CH_2–M bond. Supporting this, M–C_{aryl} bonds are known to be strong for the late transition metals, and M–C_{aryl} bond dissociation energies are comparable to or higher than those of M–H bonds.[6]

Table 1. Influence of phosphane substituents on the activation of C–C versus C–H bonds in the PCP and PCN ligands.

Metal	Ligand		C–C activation		C–H activation	
	phosphane substituent	additional phosphane	thermo. product	kinetic product	thermo. product	kinetic product
Rh	Me	PEt_3	+			+
Rh	Ph	PPh_3			+	+
Rh[a]	*i*Pr	–	+	+		
Rh	*t*Bu	–	+	+		
Ir	*t*Bu	–	+	+		
Rh	PCN[b]		+	+		

[a] S.-Y. Liou, B. Rybtchinski, D. Milstein, unpublished results. [b] *t*Bu on P, Et on N.

The role of the size of the substituents on the reaction kinetics in C–C versus C–H activation was discussed above. Bulky *t*Bu substituents shield a vacant coordination site and impose a congested conformation in a reactive intermediate that drastically lowers the kinetic barrier of C–C activation. The smaller Ph and Me substituents kinetically favor C–H activation (Table 1), which is likely to be a consequence of forming a four-coordinate intermediate.

5. Tendencies in C–C Bond Cleavage: Metals and Substrates

It is tempting to make a direct comparison between various metals regarding their reactivity in the oxidative addition of a C–C bond. However, in solution chemistry this is a task of significant difficulty, since the reported examples of C–C oxidative addition reactions involve metals in different ligand environments. Valuable information can be obtained from gas-phase chemistry.[54–57] Schwarz et al. showed that in the gas phase various naked metal ions bind molecules of the type R–X, where R is an alkyl chain and X is a functionality with a donor atom (NH_2, OH, CN), and cleave one of the alkyl C–C bonds.[55] The investigation of the product distribution using isotope labeling provides an insight into the reactivity preferences of metals for oxidative addition of C–C and C–H bonds. Thus, reactivity towards C–C bonds increases and selectivity decreases in the row Fe^+, Co^+, Ni^+. A variety of alkyl C–C bonds can be activated such as γ–δ, β–γ, and α–β C–C bonds in the R-X-M moiety. In the work by Freiser et al. a comparison of titanium and iron ions in reaction with various alkanes reflected an exclusive preference of Ti^+ for C–H activation, whereas Fe^+ was shown to be active both in C–C and C–H activation.[56] The Fe^+ ion readily inserted into any C–C bond of the alkane. So, late transition metals appear to be more active in C–C oxidative addition, the reactivity increasing on going from left to right in the Periodic Table. One should be very careful, however, in applying the gas-phase reaction aptitudes to solution chemistry. In the gas phase, unlike in solution, the M–R bond strength can be higher than for M–H.[57] Clearly, the naked metal center in the gas phase is very different from that of metal complexes in solution.

In solution C–C oxidative addition was observed for a variety of late transition metals. Most of the examples of oxidative addition of unstrained unactivated C–C bonds were demonstrated in reactions with rhodium and iridium complexes. Electron-rich Rh^I and Ir^I complexes possessing a vacant coordination site seem to be suitable for oxidative addition of unstrained unactivated C–C bonds. The only example in which a direct comparison between the reactivity of different metals with the same ligand system in solution was made is C–C oxidative addition to rhodium and iridium centers in the *t*Bu-PCP – metal system (see Section 4.6.1). Insertion into a C–C bond of the ligand was thermodynamically more favorable than into a C–H bond in the case of both metals. Kinetically, C–C activation was also slightly preferable over C–H activation in the case of both metals, rhodium being more selective for C–C activation than iridium.

No C–C cleavage was observed when various Pd precursors were used in the case of PCP and PCN ligands. It is also noteworthy that in the case of the PCN – Pt system exclusive C–H bond activation takes place.[52]

In most of the reported cases, only C–C bonds in "special" substrates can be activated by a metal complex in solution. Strained C–C bonds oxidatively add to a wide variety of the metals (see Section 3). C–C bonds adjacent to a carbonyl group (see Section 4.1) or preactivated by potential aromaticity (see Section 4.2) can be activated by various metal centers. Agostic interaction with the metal center could be supportive for C–C cleavage if the substrate is appropriately coordinated to the metal (see Section 4.3). Unstrained, unactivated C–C bonds in PCP and PCN ligands are readily cleaved due to the favorable coordination mode imposed by these ligands (see Section 4.6). Polymetal species such as clusters allow one to widen the spectrum of the substrates targeted for C–C activation (see Section 4.4).

6. Summary and Outlook

Thermodynamically, insertion into a C–C bond in solution is not a forbidden process even if no strain relief or aromatization driving force is involved (C_{aryl}–C_{Me} bonds in PCP and PCN ligands, carbonyl group adjacent to C–C,

cluster-supported C–C activation). Moreover, it can be even more favorable than competing C–H activation processes, as shown in the case of alkyl-PCP and PCN-type systems. In cases where the primary C–C oxidative addition is unfavorable, C–C cleavage may be accomplished by the use of a subsequent energy-releasing reaction, such as hydrogenolysis. C–C activation can proceed directly and does not require prior C–H activation. The competition between C–H and C–C activation in aryl-alkyl substrates is very sensitive to the electron density on the metal center, so metal complexes designed to prefer one process over the other may be designed. Coordinative unsaturation appears to be crucial for C–C oxidative addition. The "hidden" character of the C–C bonds is undoubtedly a contributing factor to this requirement. An increased naked character of ligated metal centers should be sought to achieve C–C bond cleavage in solution. An approach utilizing multimetal species (clusters and polynucleous complexes) seems promising in light of the possibility to create more orientation modes disposed for C–C bond cleavage. Another promising approach is the one based on methylene transfer.

There is only a small difference in the kinetic barriers for C–C and C–H bond activation in a system in which complexes of late transition metals possessing a vacant coordination site are brought in a close vicinity of these bonds (*t*Bu-PCP and PCN). Therefore, the *kinetic* reluctance of C–C bonds to insertion of transition metal complexes seems to be predominantly steric in nature. However, since C–C oxidative addition can be thermodynamically favorable, an important question is whether it is possible to bring unstrained, unactivated C–C bonds of substrates that are not bound to a metal through heteroatoms in close proximity of the metal center in order to achieve metal insertion, the entire process being thermodynamically driven. Such a process (inter- or intramolecular) would be of primary importance in the light of possible catalytic applications to simple organic molecules.

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