

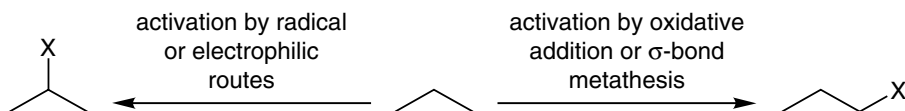
Chapter 17

C-H ACTIVATION AND FUNCTIONALIZATION OF ALKANES AND ARENES

1. INTRODUCTION

Although alkanes are considered to be inert, some classical reactions have been known for a long time, for instance with halogens, reactive radicals and superacids. The C-H bond that is cleaved in such reactions is the weakest one, i.e. reaction occurs at the most substituted carbon. Thus, the radicals R^\bullet or carbocations R^+ formed react at their most substituted carbon atom giving branched products. The selectivity in the above reactions always is: tertiary > secondary > primary.

In Chap. 3, we have examined the addition of an alkane C-H bond to a 16-electron metal center M giving a transient 18-electron metal-alkane intermediate $M(RH)$ that ultimately gives *oxidative addition* of the C-H bond to $M(R)(H)$. In this organometallic reaction, activation of the C-H bond occurs at the less substituted carbon for steric reasons. For instance, a linear alkane yields an *n*-alkyl-metal species *via* C-H activation at a terminal methyl group. The selectivity is thus primary > secondary > tertiary. This opens the valuable possibility of generating linear alkyl-functionalized products if such an oxidative addition mechanism can be made catalytic:



However, in addition to facing the functionalization of the strongest C-H bond (the terminal one) of the alkane molecule, it is necessary to overcome the fact that the monofunctional products are usually more reactive than the alkane starting material. Alcohols tend to form ketones, aldehyde and CO_2 , and monohalogenated alkanes may react further to give gem-dihalogenated products. Finally, most reactions of alkanes such as carbonylation and dehydrogenation are endergonic. Thus, in view of these problems, the goal of selective terminal alkane functionalization is very challenging. In fact, no industrial alkane functionalization process is based on alkane oxidative addition.

Yet, it is of great interest to now examine what these remarkable organometallic concepts of *oxidative addition* and *σ -bond metathesis* elaborated in the early 1980s

have brought in terms of practical catalytic functionalization of alkanes and arenes.^{17.1} It is also essential to include all the types of systems that can activate C-H bonds by metals by extending our scope to include non-classical organometallic systems, which allows comparison, mutual enrichment and confrontation of hypotheses.^{17.1}

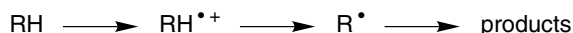
Thus, as in the case of alkenes in the preceding chapter, we start with the radical type of activation that is much older. Transition-metal compounds play a key role in radical activation, because they provide very strong oxidants that can oxidize hydrocarbons either by (reversible) electron transfer or H-atom transfer (more rarely by hydride transfer). Biological oxidation of hydrocarbons involves reactive metal-oxo species in methane mono-oxygenases and many related synthetic models, and a number of simple metal-oxo complexes also work. The clear criterion of distinction between an organometallic C-H activation and a radical activation is the above selectivity in activated C-H bonds.

Finally, as we move to arenes, it is found that C-H activation is more facile than with alkanes, because arenes are more electron rich than the latter, i.e. for instance they are easier to oxidize by single electron transfer (their oxidation potential is lower than that of alkanes), and they react more readily than alkanes with electrophiles. They can also coordinate more strongly than alkanes to transition metals, because of their ability to accept much more backbonding from transition metals than alkanes do, which facilitates further activation. Electrophilic activation of C-H bonds known from Friedel-Crafts reactions with organic electrophiles, has also been known with metal electrophiles since the end of the XIXth century and now provide really efficient catalytic C-H activation reactions. Finally, given the richness and variety of the C-H activation field, it is not surprising that organic chemists have focused on the possibility of functionalizing alkane segments in complex organic substrates, in particular *via* coordination-directed C-H bond activation.^{17.1b,c}

2. ALKANES AND CYCLOALKANES

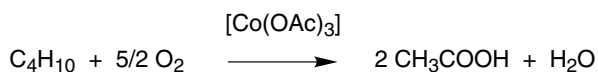
2.1. RADICAL-TYPE OXIDATION

The direct oxidation of methane and alkanes by very strong oxidants according to a single electron-transfer pathway is followed by deprotonation of the extremely acidic radical cationic species $\text{RH}^{+\bullet}$:

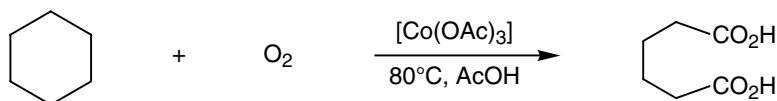


For instance, peroxodisulfate oxidizes methane to alcohols in the absence of a metal at 105–115°C. Metal complexes can be used as mediators for such reactions which permits carrying out the reactions at lower reaction temperatures.^{17.1} In the case of cycloalkanes, strongly electrophilic and oxidizing transition-metal ions play an irreplaceable role in the initiation step.

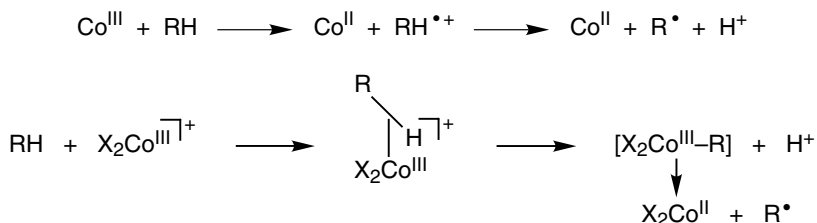
Butane can be oxidized with O_2 to acetic acid at $180^\circ C$ under pressure using Co^{3+} as catalyst, but other acids are also obtained in the reaction medium. This industrial process has been abandoned in favor of the Monsanto process starting from methanol.



Likewise, cyclohexane is oxidized by O_2 to adipic acid (*via* cyclohexyl hydroperoxide, cyclohexanol and cyclohexanone). Adipic acid, which was used for the synthesis of nylon-6,6 by DuPont de Nemours, is now produced from butadiene (see Chap. 15.5).



The accurate mechanism of this type of reaction is still uncertain, however. For instance, in the first step, the formation of the radical R^\bullet from the hydrocarbon RH , it is difficult to distinguish between a single-electron oxidation (outer-sphere mechanism without formation of bond) and an electrophilic attack (inner-sphere mechanism involving intermediate coordination). In both hypotheses, the cationic species formed is extremely acidic and immediately loses a proton to form the neutral radical:



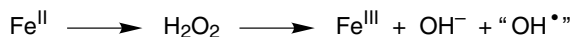
In the second hypothesis, a C-H bond of RH is a 2-electron L ligand for the metal, analogous to the dihydrogen ligand H_2 (although weak and distorted because of the steric bulk of R). The H_2 complexes are acidic, and so are the alkane complexes.

An example of typical H-atom abstraction from alkanes following the selectivity trends observed for radical reactions was discovered by Crabtree using photo-excited Hg atoms in the gas phase. The reaction applies not only to alkanes, but also to alcohols, ketones, amines, etc.



with RH = alkane, alcohol, ketone, amine, etc.

Let us end this section by considering the Fenton reaction, discovered in the 1890s, whereby Fe^{II} salts catalyze the hydroxylation of alkanes and other substrates. In these systems, iron (II) salts reduce H_2O_2 to OH^- and supposedly “ OH^\bullet ” that is assumed to subsequently abstract a hydrogen atom from the substrates: ^{17.3}

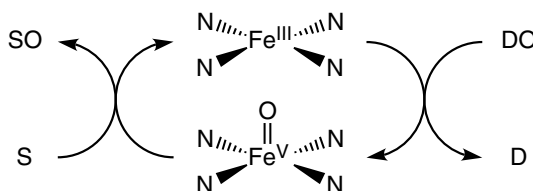


This system is of industrial importance and biological interest because of the cytotoxicity of the generated oxygen species.^{17.3,17.4} Since OH^\bullet is of extremely high energy, however, it is unlikely for this very thermodynamic reason, that it be liberated in the free state (especially in the presence of iron salts). Indeed it has been proposed that inner-sphere OH transfer may intervene *via* an Fe-OH species.^{17.3b} If we refer to the following section and to Chap. 19 which is devoted to Fe-based methane monooxygenase sites and their models, one realizes that Fe-OH is a protonated form of the ferryl species $\text{Fe}=\text{O}$, and therefore it is probable that Fenton chemistry is relevant to the biological alkane activation systems.^{17.4a}

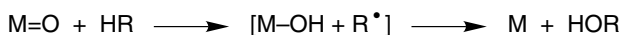
2.2. HYDROXYLATION

USING METHANE MONOOXYGENASE MODELS AS CATALYSTS

Metal-porphyrin complexes (noted N_4M in the scheme below, see Chap. 1) are able to catalyze the transfer of an oxygen atom to an alkane RH giving an alcohol ROH , the donor substrate being PhIO (iodosylbenzene), H_2O_2 , NaOCl , KHSO_5 , etc.^{17.4-17.6} Such systems mimic the monooxygenase enzymes whose function is examined in Chap. 19. The metal can be Fe^{III} , Ru^{II} or Mn^{III} . The simple porphyrin ligands are themselves attacked, but perchlorinated porphyrins are not. Other substrates S are also mono-oxygenated in the same way to SO : these are olefins (to epoxides), phosphines, amines and sulfides to the corresponding oxides. The intermediate $\text{M}=\text{O}$ species are very reactive. In the case of Fe, the mesomeric iron-oxyl form $\text{Fe}^{\text{IV}}-\text{O}^\bullet$ has a slightly greater energy (3 to 5 kcal higher) than the $\text{Fe}^{\text{V}}=\text{O}$ form.



This mechanism represents a shortcut in biological mono-oxygenase enzyme systems that use O_2 as oxygen atom sources and whose mechanism is much more complex because of the requirement to cleave O_2 . Non-porphyrinic binuclear methane mono-oxygenase model complexes are also able to activate methane in the same way (see Chap. 19).^{17.7} When $\text{S} = \text{RH}$, Groves originally proposed the well-known “rebound” mechanism in which the $\text{Fe}^{\text{V}}=\text{O}$ species removes an H atom from RH , then transfers OH^\bullet to produce the alcohol ROH :^{17.4}



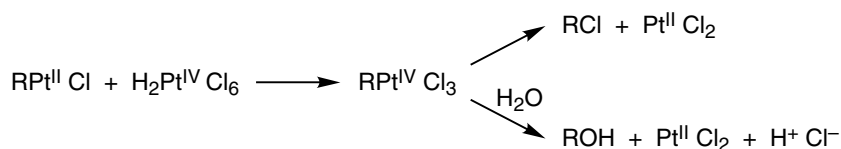
This mechanism has been the subject of considerable debate,^{17.4-17.6} and the first step, which consists in an overall H-atom transfer, may in fact, be an electron transfer followed by a stepwise proton transfer or an inner-sphere H-atom transfer in the cage or any intermediate along the continuum between the two situations.^{17.8}

2.3. FUNCTIONALIZATION VIA ACTIVATION BY Pt^{II} : SHILOV CHEMISTRY

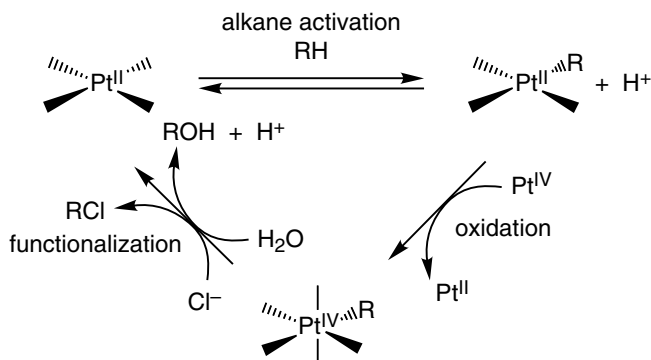
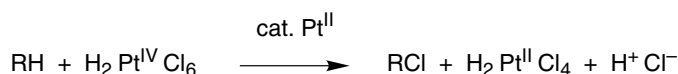
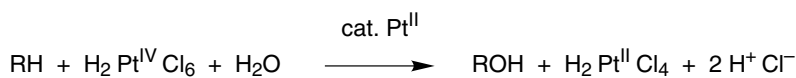
In Chap. 3.3.7.4, it was indicated that a mixture of $PtCl_2$ and H_2PtCl_6 activates methane and alkanes, *via* the intermediacy of a Pt-alkyl species which is formed either by direct deprotonation of the transient Pt^{II} -alkane complex or by oxidative addition of the alkane ligand within this complex giving a Pt^{IV} -alkyl-hydride intermediate.



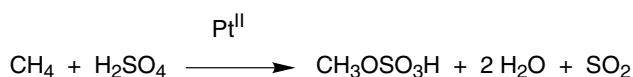
This remarkable activation system, which was discovered in 1969 by Shilov,^{17,9} was ignored for more than a decade. The reaction is catalytic in $PtCl_2$ but only stoichiometric in $H_2Pt^{IV}Cl_6$. A revival of interest starting in the 1980s has contributed to gaining insight into the details of the mechanism using model complexes.^{17,10-17,12} The role of $H_2Pt^{IV}Cl_6$ is to re-oxidize $Pt^{II}-R$ to $Pt^{IV}-R$ in each catalytic cycle, as demonstrated by Bercaw and Labinger.^{17,10} Nucleophilic attack on the carbon atom of the $Pt^{II}-R$ bond by H_2O or Cl^- (shown by stereochemical inversion at carbon) finally produces methanol or methyl chloride respectively (equations below, $R = CH_3$ or alkyl).^{17,10} In model complexes, strong evidence has been provided by the Bercaw-Labinger^{17,10} and Goldberg^{17,11} groups that this nucleophilic attack occurs at five-coordinate Pt^{IV} rather than six-coordinate Pt^{IV} .



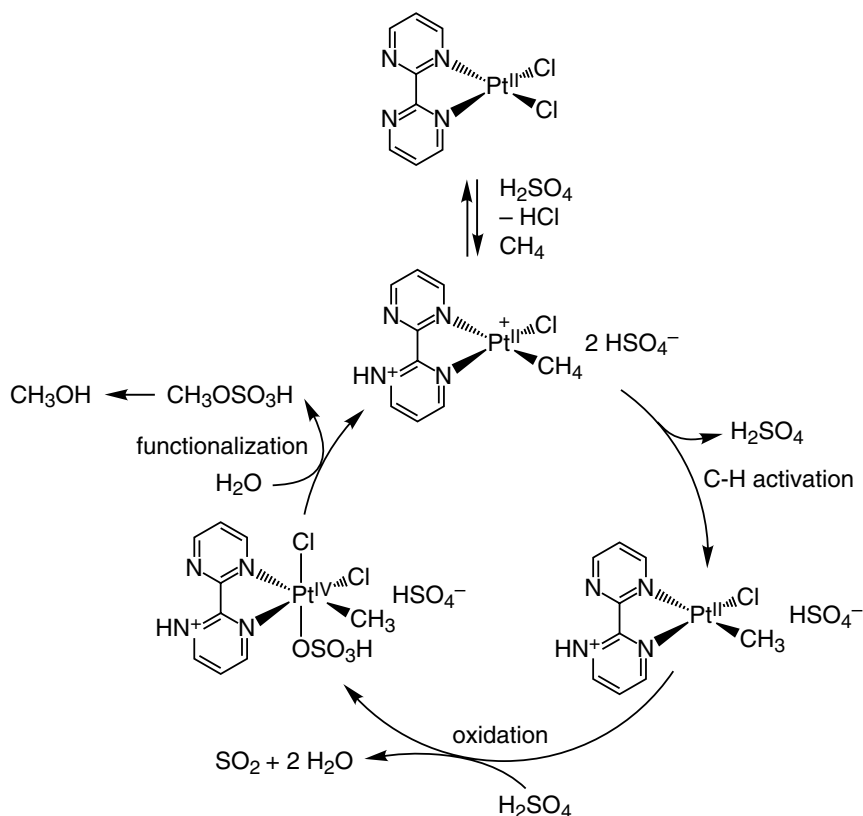
The overall stoichiometries and mechanism proposed by Shilov are as follows:^{17,9}



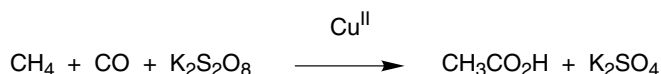
Related systems using less expensive alternative stoichiometric oxidants have been disclosed.^{17.13-17.16} One of the most significant developments was found at Catalytica by Periana using SO_3 in fuming H_2SO_4 , which acts as both the solvent and the stoichiometric oxidant. The Pt^{II} complex $[\text{PtCl}_2(\text{bpym})]$ is used as the catalyst for this process (see below). Methylbisulfate is obtained in 72% yield with 90% conversion of methane and 81% selectivity, and the turnover numbers are greater than 300. The catalyst is inhibited by H_2O or methanol, causing low reaction rates below 90% H_2SO_4 . This process is thus remarkably efficient, although not economically competitive compared with existing heterogeneous industrial processes. The mechanism is similar or very closely related to that of the Shilov system (i.e., it is not clear whether oxidative oxidation or σ -bond metathesis is the methane C-H activation step):^{17.13}



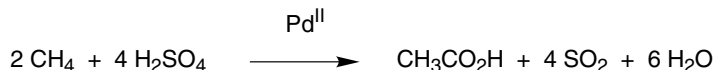
Proposed mechanism for the Catalytica methane oxidation system:



Among other remarkable developments, it should be noted that the carboxylation of methane can be coupled with oxidation by potassium peroxysulfate in trifluoroacetic acid to yield acetic acid, the reaction being catalyzed by $\text{Cu}(\text{OAc})_2$.^{17.15}

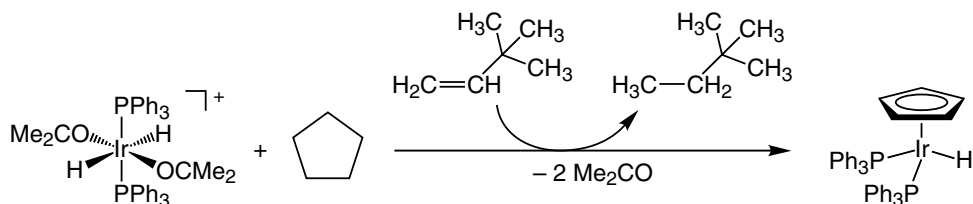


Interestingly, carbonylation can also proceed in the absence of CO, although in only 10% yield, using PdSO_4 as the catalyst in concentrated sulfuric acid as solvent and oxidant:^{17.16}

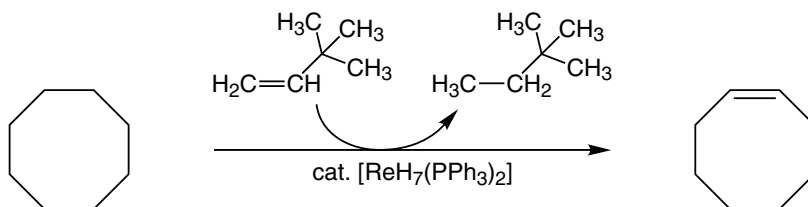


2.4. DEHYDROGENATION INVOLVING OXIDATIVE ADDITION

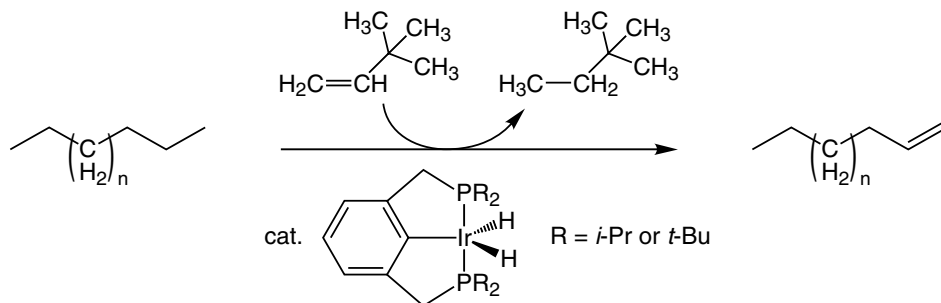
Oxidative addition is probably the most powerful concept of organometallic chemistry, and it has been applied in the preceding chapters to hydrogenation and hydroelementation of olefins and in the last chapter to catalysis of organic halide functionalization. We know that oxidative addition of alkanes is much more difficult than that of many substrates, however, and only known in few cases. Thus, its implication in catalysis is extremely challenging, and therefore the discovery by Crabtree in 1979 that cyclopentane and cyclooctane can be dehydrogenated by $[\text{Ir}(\text{Me}_2\text{CO})_2\text{H}_2(\text{PPh}_3)_2]^+$ to the corresponding alkadiene was a real breakthrough.^{17.17} This was reversing the transition-metal catalyzed hydrogenation of alkenes to alkanes, and indeed the mechanism was proposed to start by oxidative addition of the cycloalkane to a cycloalkyl-metal-hydride species. The reaction was carried out in the presence of a good hydrogen acceptor, ideally *t*-butylethylene, in order to compensate the endergonicity ($\Delta H = 30 \text{ kcal} \cdot \text{mol}^{-1}$) of the dehydrogenation of the alkane to the free olefin and H_2 .



A year later, the dehydrogenation of cyclooctane to cyclooctene was made catalytic by Felkin's group with the complex $[\text{ReH}_7(\text{PPh}_3)_2]$,^{17.17b} (equation below) and Crabtree showed that alkanes can also be catalytically dehydrogenated using the complex $[\text{Ir}\{(\text{CF}_3)_2\text{CO}\}_2\text{H}_2(\text{PPh}_3)_2]^+$.

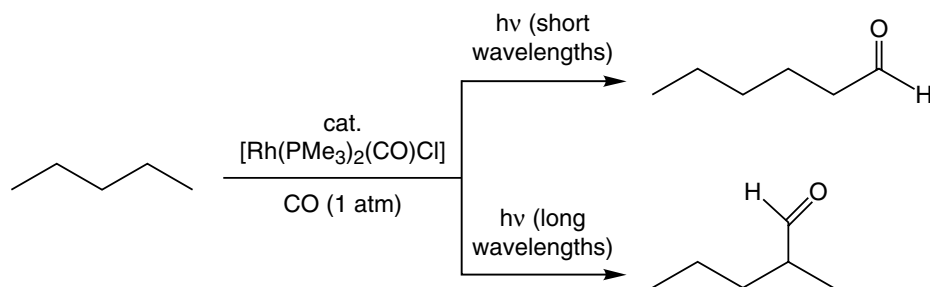


Futhermore, Goldman has found a complex that features a pincer ligand and is the most efficient catalyst for alkane dehydrogenation.^{17.19a} Double bonds can be introduced into polymers and dehydrogenation of tertiary amines leads to enamines.^{17.19b}

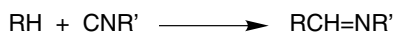


2.5. CARBONYLATION INVOLVING OXIDATIVE ADDITION

Tanaka reported that alkanes can be catalytically carbonylated to aldehydes under 1 atm of CO using the catalyst [*trans*-Rh(PR₃)₂(CO)Cl].^{17.20} This disclosure (with R = Me) followed the report by Eisenberg of the carbonylation of benzene to benzaldehyde under the same conditions but using the related catalyst in which R = Ph (see section 3.4.1).^{17.21} The electron-rich phosphine PMe₃ facilitates oxidative addition of the alkane by increasing the electron density on the rhodium center, compared with PPh₃. These reactions would normally be endergonic, but when carried out under photochemical conditions, they are exergonic, since light drives them in each catalytic cycle. A puzzling feature of alkane carbonylation is that, with short wavelength radiation, *n*-alkanes are carbonylated regioselectively at the terminal position whereas with longer wavelengths, branched aldehydes are regioselectively obtained. It has been proposed that long wavelength radiation effected photo-elimination of CO followed by C-H oxidative addition, whereas short-wavelength light induced both direct C-H oxidative addition to the photo-excited state of the starting complex and alkyl-to-CO migratory insertion. Apparently, the 4-coordinate species is more sensitive to steric factors; hence the regioselectivity:^{17.22}



Other similar insertions of unsaturated bonds into alkane C-H bonds include aldimines whose insertion is catalyzed by d⁸ complexes (Fe⁰, Ru⁰, Rh^I):^{17.23}



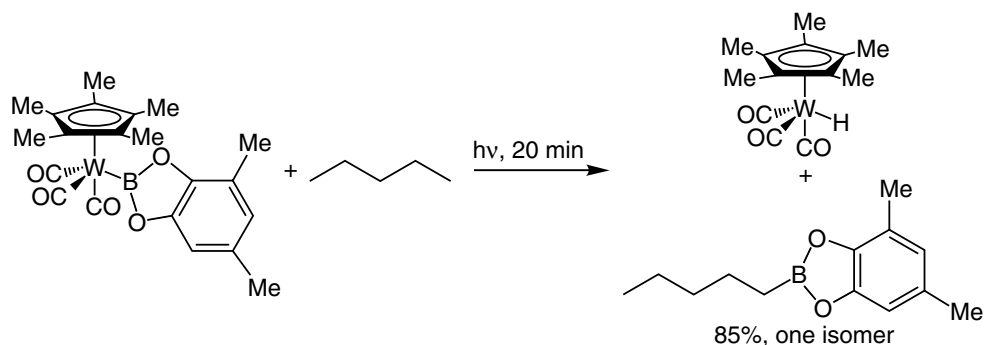
2.6. REGIOSELECTIVE BORYLATION INVOLVING σ -BOND METATHESIS

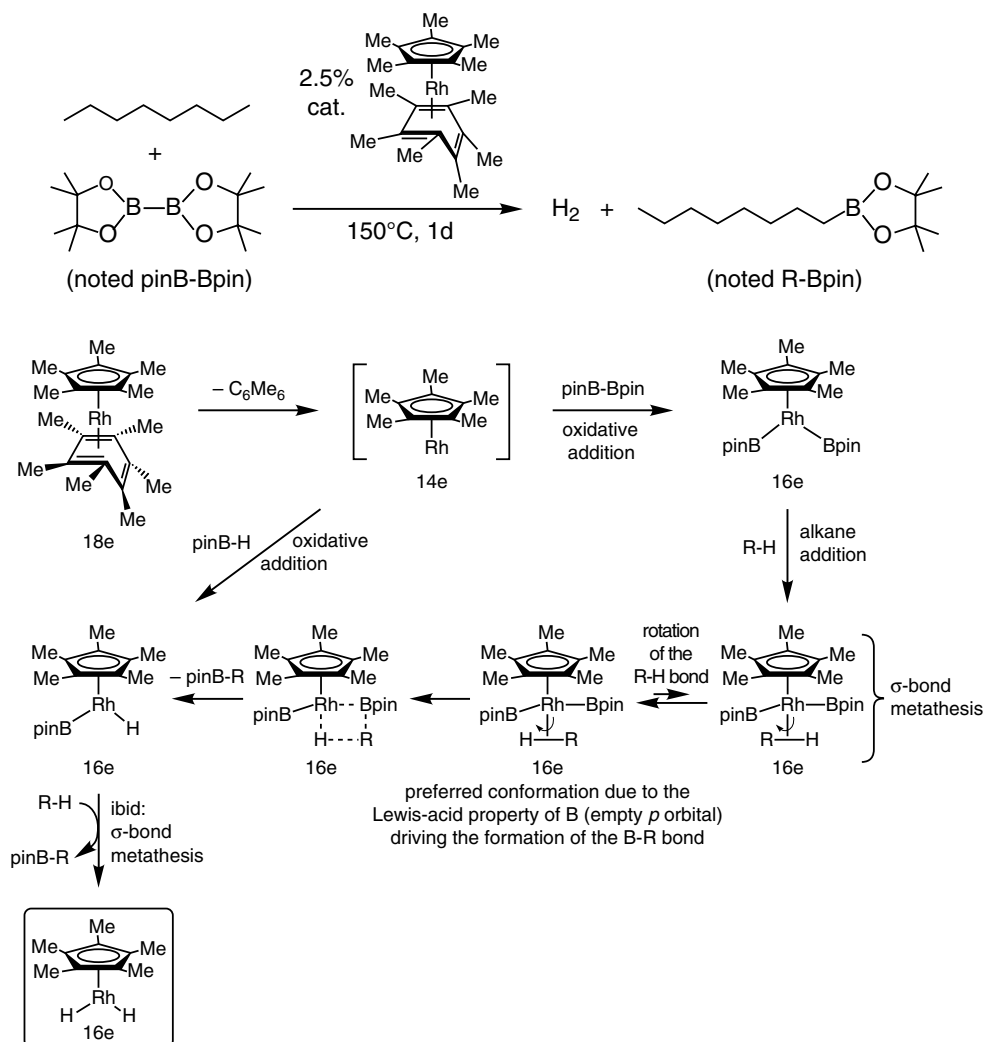
After having shown that various transition-metal-boryl complexes react with alkanes under photochemical or thermal conditions to produce alkyl-boron compounds (first equation below),^{17,24a} Hartwig discovered that diboron compounds also react regioselectively with alkanes to afford alkyl-boron compounds in good to excellent yields, these reactions being catalyzed by organotransition-metal complexes.^{17,24b-e} The catalytic reactions proceed by ligand loss (upon irradiation^{17,24b} or heating^{17,24c}) from an 18e complex to produce a transient 16e intermediate. The latter effects the oxidative addition of the diboron compound such as bis-pinacoldiborane to generate a transition-metal-boryl bond that resembles the one shown below in the stoichiometric reaction (with a different metal). Alternatively, starting from HB (pinacolate) also provides this bond. The catalyst used under photochemical conditions is $[\text{Cp}^*\text{Re}(\text{CO})_3]$,^{17,24b} whereas those used under thermal conditions are $[\text{Cp}^*\text{IrH}_4]$, $[\text{Cp}^*\text{Rh}(\text{C}_2\text{H}_4)_2]$, $[\text{Cp}^*\text{Rh}(\text{C}_6\text{Me}_6)]$ and $[(\text{Cp}^*\text{RhCl})_2]$.^{17,24c,e}

The reactions typically proceed at 150°C with *n*-octane and di-pinacoldiborane for 5-24 h, and the amount of catalyst typically is 1-5%. The yields of 1-octylboronate ester are good and the reaction is regioselective in the terminal alkyl position (second equation below, top of p. 418). The proposed mechanism involves oxidative addition of the B-B or B-H bond, followed by σ -bond metathesis between the M-B and R-H bonds, which is driven towards formation of the B-R bond by the Lewis-acid property of boron. Note that 16e species (see Scheme p. 418) could also be involved in oxidative addition of the alkane to give an 18e intermediate $\text{M}(\text{Bpin})_2(\text{H})(\text{R})$ or $\text{M}(\text{Bpin})(\text{H})_2(\text{R})$ that would provide R-Bpin as well by reductive elimination. Calculations showed, however, that the σ -bond metathesis path is preferred by about 10 kcal \cdot mol⁻¹ over this alkane oxidative-addition path.

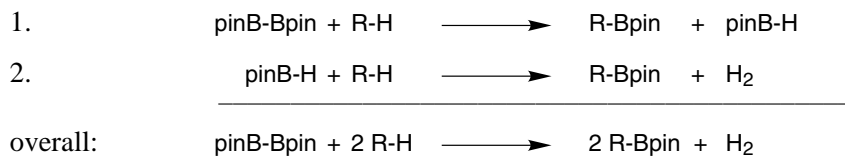
The strength of the B-C bond (111-113 kcal \cdot mol⁻¹),^{17,24d} which is larger than that of a terminal alkane C-H bond, is responsible for the driving force of the overall reaction, and the lack of a β -hydrogen atom in the pinacolboryl group inhibits side reactions of the metal-boryl intermediates. Altogether, this remarkable catalytic regioselective borylation of alkanes is probably the most efficient and useful process so far for regioselective alkane functionalization.^{17,24e}

Example of stoichiometric alkane borylation:



Example of catalytic alkane borylation:

Generation of the catalytically active $\text{Cp}^*\text{Rh}(\text{H})_2$ species from the precatalyst $\text{Cp}^*\text{RhC}_6\text{Me}_6$ by oxidative addition of either pinB-Bpin or H-Bpin (pin = pinacolate, see above) followed by σ -bond metathesis of the Rh-B and R-H bonds

Proposed catalytic cycle for alkane borylation:



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