C–H activation

C–H activation is mechanistically similar to the reaction of H–H with metal complexes. It can occur through oxidative addition, sigma-bond metathesis, metalloradical activation, 1,2-addition, or electrophilic activation.

Oxidative addition

\[ \text{M}^{(n)} \text{R} \rightleftharpoons \text{M}^{(n+2)} \text{R} \]

Sigma-bond metathesis

\[ \text{M} \rightleftharpoons \text{R} \text{H} \rightleftharpoons \text{M} \rightleftharpoons \text{R} \text{H} \]

1,2-Addition

\[ \text{M} \rightleftharpoons \text{C} / \text{N} \text{R} \rightleftharpoons \text{M} \rightleftharpoons \text{C} / \text{N} \text{R} \]

Metalloradical activation

\[ 2 \text{M}^{(n)} \text{R} \rightleftharpoons \text{M}^{(n+1)} \text{R} \rightleftharpoons \text{M}^{(n+1)} \]

Electrophilic metallation

\[ \text{M}^+ \text{X}^- \rightleftharpoons \text{Ar} \rightleftharpoons \text{M} \rightleftharpoons \text{Ar} \text{H}^+ \text{X}^- \]

Oxidative addition typically occurs with electron-rich, low-valent complexes of late transition metals such as Re, Fe, Ru, Os, Rh, Ir, Pt. The reaction starts with generation of a coordinatively unsaturated complex thermally or photolytically to enable the coordination of a C–H bond to the metal center.

Intramolecular engagement is a common strategy to enhance C–H σ-coordination. The term “agostic interaction” was coined by Brookhart and Green in 1983, and redefined by Scherer and McGready in 1994 to refer to “distortion of an organometallic moiety which brings an appended C–H bond into close proximity with the metal center.” Interaction of a lone pair or π electrons with the empty d orbitals can also facilitate this weak interaction, making oxidative addition of C(sp²)–H easier than that of C(sp³)–H. Complexes with “intermolecular” σ-coordination of a C–H group to metal can be generated by photolytic dissociation of a ligand in the presence of an alkane or protonolysis of a metal-alkyl complex.
Unusually short M–H distances have been observed as early as 1965 by Ibers, and Cotton proposed a three-center-two-electron M–H–C bond for a molybdenum complex in 1974.

Williams used X-ray and neutron diffraction in 1980 to confirm a nonlinear configuration of M–H–C in a cationic iron complex. The Fe–H distance is only 1.874 Å and the hydrogen atom occupies the sixth coordination site of a distorted octahedron of the otherwise formally 16-electron Fe center. The C–H distance is 1.164 Å, significantly longer than those observed before. Green also prepared a sterically unhindered titanium alkyl complex to demonstrate the agostic interaction in 1982. Because the titanium center is $d^0$ configured, it has empty orbitals to interact with $\sigma$-C–H.

The agostic interaction should not be confused with the anagostic interaction that is typically associated with square planar $d^8$ transition metals. Anagostic interactions range from purely electrostatic to electrostatic with partial covalence. An extreme view will be a three-center-four electron hydrogen bond interaction; however, the $d_{z^2}$ orbital is not involved to a significant degree.

Agostic interactions are best characterized by crystallographic studies. The C–H and M–H bond distances are about 5-20% longer than usual based on neutron diffraction studies. The typical M–H distance is 1.8–2.3 Å and the M–H–C angle is 90°–140°.

The $^1$H NMR chemical shift of an agostic C–H has an upfield shift and is close to that of a metal hydride. The $^1J_{CH}$ value (70–100 Hz) is also smaller than that of a normal sp$^3$ C–H (125 Hz). A lower C–H stretching frequency in IR (<2800 nm$^{-1}$) due to a weakened C–H bond is also indicative of an agostic interaction. However, some metal complexes show agostic interactions in solid states but no characteristic $^1$H NMR and IR peaks. Agostic interaction is stronger than hydrogen bonds and can provide ~10 kcal/mol of stabilization and plays an important role in stabilizing reactive species and transition states.
Brookhart argues that many of the proposed 16-electron intermediates are in fact 18-electron agostic complexes and the 16-electron species are transition states. In the titanium(IV)-catalyzed Ziegler–Natta olefin polymerization reaction, the migratory insertion is facilitated by an α-agostic interaction in both ground state and transition state. The involvement of an agostic interaction in the transition state can be probed by secondary kinetic isotope effect.

An agostic interaction involves a strong enough σ-donation but a weak metal backbonding. When the backbonding is too strong, cleavage of the C–H bond occur to form the oxidative addition product. Crabtree has used structural data of agostic complexes to construct the trajectory of the oxidative addition of R–H through intermolecular attack of a C–H bond by a metal complex.

Watson reported in 1983 that lutetium and yttrium metallocenes could undergo degenerative alkyl ligand exchange. Because these metal alkyl or hydride complexes is $d^0$ configured, they could not undergo oxidative addition. Watson proposed a four-centered transition state based on the kinetics of methane exchange. This type reversible reaction is more common for group 3 metals (Sc, lanthanides and actinides) but an also occurs with group 4 and group 5 metals. However, redox reaction of group 4 metals complexes could occur through redox-noninnocent ancillary ligands. α-Bond metathesis of a C–C bond has not been reported.

Due to the strong interaction between the metal center and the β-atom, the transition state involves a kite-like, distorted $[2\sigma + 2\sigma]$ cycloaddition. The empty orbitals help relax the symmetry requirement to allow for the otherwise symmetry-forbidden reaction. Thus, the four-centered transition state does not involve a charge-separated heterolytic cleavage of hydrogen. For lanthocene complexes, the transition state is more polarized, suggestive of a proton-transfer reaction. In contrast, α-bond metathesis of scandium complexes has a non-polar transition state.

As the more s character the better orbital overlap, the reaction rate goes by C(sp)–H > C(sp$^2$)–H > C(sp$^3$)–H; however, there is no substitution effects. Additionally, primary C(sp$^3$)–H reacts faster than secondary for steric reasons. More electropositive metal centers are more reactive. The reactivity for group 3 metal is Lu >> Y > Sc.
Scandocene alkyl and aryl complexes react with ethylene, propene, and internal alkynes by insertion, but with longer alkenes and terminal alkynes by σ-bond metathesis. σ-Bond metathesis also provides a way to terminal the chain reaction. Harrod reported in 1985 that dialkyl titanocene complexes can catalyze silane dehydropolymerization to give polysilanes with unusual electronic properties such as σ-conjugation. Later, Tilley provided evidence for the σ-bond metathesis mechanism. For reacting with silanes, the silicone atom can take either the α or β-position in σ-bond metathesis. When the more reactive electropositive catalysts are used, redistribution of silane occurs to give lower molecular weight of the polymer.

Catalytic dehydrocoupling via σ-bond metathesis can also be applied to stannanes, germanes, phosphines, and arsines. Additionally, heterodehydrocoupling of silanes and phosphines has also been reported. σ-Bond metathesis is also useful for catalytic hydrogenation, hydroamination, hydrophosphination, hydrosilation, and hydrothiolation of olefins. Jordan reported in 1989 a zirconium-catalyzed C–H insertion reaction wherein an olefin is incorporated onto the 6-position of 2-picoline via σ-metathesis. Addition of hydrogen helps cleavage of the Zr–C bond after olefin insertion. There is no turnover in the absence of hydrogen which should be considered as a cocatalyst instead of a reagent.
Tilley reported in 2003 that a scanocene alkyl complex can catalyze hydromethylation of olefin. He found that Cp*₂ScCH₂C(CH₃)₃ prepared by reacting Cp*₂ScCl with LiCH₂C(CH₃)₃ can react with the C–H bonds of benzene, cyclopropane, and even methane through σ-bond metathesis. Reaction of Cp*₂ScCH₂C(CH₃)₃ with methane gives Cp*₂ScCH₃ that enters the catalytic cycle. Although the activation enthalpy (ΔH*) is only 11.4 kcal/mol, intermolecular competing experiment using CH₄/CD₄ gave a kinetic isotope effect value of 10.2, while intermolecular competing experiment using CH₂D₂ gave 5.4. He later found that introducing a dimethylsilyl ansa-bridge leads to up to two order of magnitude improvement in activity partly due to faster methane C–H bond activation. This new catalyst enables the hydromethylation of exo-methylene species to give a gem-dimethyl-containing quaternary center.

Alkane can also react with an early transition metal imido or alkylidene species through 1,2-addition. Wolczanski and Bergman first reported in 1988 that imidozirconium complexes can react with hydrocarbons by C–H activation. For example, thermolysis of an alkyltriamidozirconium species induced a 1,2-elimination to give a transient imido species that reacted with the hydrocarbon solvent by 1,2-addition. Cyclohexane is inert to this reaction presumably due to higher steric hinderance. Legzdins found in 1997 that a transient tungsten alkylidene complex could also undergo a reversible 1,2-addition reaction.
Wayland reported in 1990 that \( ^* \text{Rh}(\text{TMP}) \) reacts with methane in benzene to give rhodium hydride and methyl complexes (\( \text{TMP} = \text{tetramesitylporphyrhato} \)). \( [\text{Rh}(\text{TXP})]_2 \) having a Rh–Rh bond dissociation energy of 12 kcal/mol is also an active catalyst (\( \text{TMP} = \text{tetraxylylporphyrhato} \)) upon homolysis. Kinetic and thermodynamic studies suggest that this reaction proceed through a metalloradical mechanism. Because the Rh–H bond strength is only about 60 kcal/mol, direct C–H abstraction by rhodium to generate a free alkyl radical would be endothermic by about 45 cal/mol. It is more likely that this reaction proceed through a \( [\text{Rh}–\text{H}–\text{C}–\text{Rh}] \) four-center transition state. Zhang has also reported a metalloradical reaction for C–H nitrogenation but the transition state involves only one Co-catalyst and the C–H abstraction was mediated by a N-centered radical.

Unlike oxidative addition, electrophilic metatllation does not involve a change of oxidation state during M–C bond formation. Typically a highly polar solvent is used and the more electron-rich arenes has higher reactivity.

\[
\begin{align*}
L_n\text{MX}_n & \rightleftharpoons L_n\text{MX}_{n-2} \\
R–H & \rightarrow \text{HX} \rightarrow R–X & \text{HX}
\end{align*}
\]

Winstein suggested in 1955 that electrophilic mercuration of arene involves a concerted metatllation–deprotonation mechanism. Olah studied the structure of arenemercurinium ion by NMR in 1976 and found it exists in an equilibrium of \( \sigma^- \) and \( \eta^2 \pi^- \) complex. The kinetic studies carried out by Roberts in 1980 supported the the concurrent C–H bond cleavage and C–Hg bond formation mechanism although the SEAr mechanism could not be completely ruled out. The \( \eta^2 \pi^- \) coordination mode has been validated by X-ray analysis.
Garnett reported in 1958 that heterogeneous platinum catalysts promote H/D exchange. He subsequently showed in 1967 that sodium and potassium tetrachloroplatinate(II) catalyze exchange of aromatic hydrogen atoms with the proton of water and acetic acid. Additionally, sodium hexachloroiridate(III) and Rh(III) chloride can also catalyze H/D exchange of alkanes. This metal-catalyzed H/D exchange reaction works for both activated and unactivated C(sp²)–H and C(sp³)–H, providing a convenient way for isotope labeling.

Based on the H/D exchange reaction developed by Garnett, Shilov found in 1969 that platinum(II) salts can catalyze H/D exchange of alkane in aqueous acid media. He then reported in 1972 that potassium platinum(II) chloride catalyzes the reduction of potassium platinum(IV) chloride by cyclohexane in 70% aqueous trifluoroacetic acid with the formation of benzene, chlorobenzene, and cyclohexyl chloride. Reduction of other hydrocarbons, including methane, can also be achieved with this catalyst system. Additionally, he found that ruthenium(IV) complexes catalyze C–H oxidation by chromic acid, and Cu(II) complexes catalyze H/D exchange in water.

For the classic Shilov system, the activity of platinum catalyst goes by (Sol)₂PtCl₆ > (Sol)PtCl₃ > PtCl₄²⁻, and with soft ligands retarding the reaction: CN⁻ ≈ CNS⁻ < PPh₃ < DMSO < pyridine < NO₂⁻ < I⁻ < Br⁻ < NH₃ < Cl⁻ < H₂O ≈ F⁻ ≈ SO₄²⁻. Aqueous media increases the electrophilic reactivity of soft cations. However, a stoichiometric amount of potassium platinum(IV) chloride is also needed as the oxidant in this reaction, limiting its practical use. This Shilov system did not receive attention in the West until late 1980s.
Several model systems have been developed by Labinger, Bergman, Bercaw, and Jones to study the Shilov system. The rate-limiting step is associative displacement of a solvent ligand by C–H. Platinum(II) chloride is an electrophilic metal complex that interacts with alkane mainly by C–H σ-donation with weak backboning. The oxidative addition to give an alkyl(hydrido)Pt specie is fast. Whereas often termed “electrophilic activation”, ligands that render the Pt center more electrophilic retard the reaction due to stronger water coordination. Computation studies on the dominant Shilov species PtCl$_2$(H$_2$O)$_2$ in aqueous solution suggest that cis-PtCl$_2$(H$_2$O)(η$^2$-CH$_4$) is more stable than the trans isomer, the barrier to C–H cleavage is only ~6 kcal/mol, and the resulting Pt–H is highly acidic (pKa ~ −5).

Oxidation of by a platinum(IV) salt proceeds through inner-sphere electron-transfer with a highly negatively charged bridged intermediate. The rate of oxidation is very rapid giving no protonolysis of Pt–C at high temperature. Nucleophilic attack of the methyl group by water gives methanol and regenerates the catalyst. Metallic Pt forms due to the close redox potential of the Pt(II)/Pt(IV) and Pt(0)/Pt(II) cycles giving <20 turnover number with <10$^5$ s$^{-1}$ turnover frequency.

Sen reported in 1987 that palladium(II) salts can oxidize methane to give methyl trifluoroacetate. He further found in 2001 that copper(II) chloride is a cheaper oxidant and can be used in a catalytic amount with oxygen being the terminal oxidant. The copper-modified Shilov system catalyzes hydroxylation with moderate to good selectivity for primary C–H. Moiseev also reported in 1990 that cobalt(III) salts are effective catalysts for methane oxidation by air.
Periana has designed several soft cationic systems, including mercury(II), platinum(II), palladium(II), gold(I/III), and thallium(III), for the functionalization of methane since 1993. Built upon Rudakov’s “acid direction”, he used sulfuric acid as an inexpensive, stable solvent to activate the catalyst through ligand protonation, and deactivate the alcohol product by protonation. Whereas simple platinum salts have poor stability and solubility in sulfuric acid, cisplatin and transplatin Pt(NH$_3$)$_2$Cl$_2$ are effective catalysts that are soluble and moderately stable in concentrated sulfuric acid. These $\sigma$-amido platinum complexes has a half-life time of 15 min at 180 ºC.

In contrast to the mercury catalyst system, the ligated platinum system can operate in the presence of excess sulfur trioxide without the formation of methanesulfonic acid (CH$_3$SO$_3$H). To prevent the complex from acid-promoted ligand dissociation, Periana used $\kappa^2$-2,2′-bipyrimidyl ligand in 1998 and observed over 300 turnovers at 200–250 ºC without catalyst deactivation. This Catalytica system is arguably the most effective platinum catalyst for C–H oxidation with oleum being the oxidant and solvent. However, oxygen cannot be used directly as the terminal oxidant although sulfur trioxide can be regenerated from sulfur dioxide through air-oxidation as a separate process. Additionally, the reaction rate is relatively low and the bisulfate byproduct inhibits the reaction at ~1 M.
The synthetic utility of Shilov chemistry has been investigated by Sames briefly. He reported in 2001 that the $\text{K}_2\text{PtCl}_4/\text{K}_2\text{PtCl}_6$ system catalyzed the $\gamma$-oxidation of valine selectively with at least 1.3 TON. Using CuCl$_2$ as the oxidant improved the TON but led to decreased diastereoselectivity.

The reaction is believed to proceed through chelation of the amino acid to the Pt(II) complex. Consistently, no reaction occurred with proline wherein the cyclic structure prevents the Pt center to reach its C–H groups. Simple carboxylic acids but not valine can be oxidized by CuCl$_2$ and Na$_2$S$_2$O$_8$ to give $\gamma$-lactones, suggesting that the platinum(II)-catalyzed oxidation of valine did not proceed through a free radical mechanism with a carboxyl radical intermediate.

In addition to valine, a variety of amino acids as well as simple amines and carboxylic acids can also be oxidized at the $\gamma$- and $\delta$-positions selectively. Sanford showed in 2015 that selective hydroxylation at the terminal position of $N$-alkylpyrrolidines can be achieved by the copper-modified Shilov system in good yields.
The oxidative addition of C–H to metal is favored for $d^8$ metals with electron-rich ligands. For example, Chatt reported in 1965 that reduction of RuCl$_2$(dmpe)$_2$ by sodium naphthalide gave Ru(dmpe)$_2$, an electron-rich 16-electron complex that underwent facile C–H insertion. Nevertheless, other metal configurations are also reactive. Green found in 1970 that photolysis of Cp$_2$WH$_2$ with benzene gave Cp$_2$W(Ph)(H) through $d^4$ Cp$_2$W.

Crabtree reported in 1979 that [IrH$_2$(PPh$_3$)$_3$(acetone)$_2$]BF$_4$ can dehydrogenate alkanes to give alkenes. However, the product is a better ligand than the substrate. Introduction of a sacrificial H$_2$ acceptor allows for catalyst turnover, but isomerization of the initially formed terminal olefin occurs to give various unsaturated products. Later, Jensen and Goldman used pincer ligands to improve thermal stability and control of the steric and electronic properties of the metal. These PCP complexes can catalyze dehydroaromatization of $n$-alkanes and oxidation of ketones to enones.
Bergman and Graham reported in 1982 intermolecular addition of alkane C-H bonds. Bergman further provided evidence for oxidative addition of unactivated C-H to a homogeneous Ir or Rh metal center. UV-irradiation of Cp*(PMe)_3IrH_2 in saturated hydrocarbons leads to extrusion of H_2 and production of Cp*(PMe)_3Ir(R)(H).

The reaction of Rh complexes is more exothermic than that of the Ir complexes. The complexation energy is ~10 kcal/mol and activation barrier only 4.6 kcal/mol for the insertion of the σ-coordinated Cp*Rh(CO)(C_6H_12). Insertion to the less hindered but stronger C-H bond (sp^2 > 1° > 2° > 3°) is both kinetically and thermodynamically favored.

In contrast to the Shilov system, the 16-electron CpML species is nucleophilic, providing strong π-backboning as compared to σ-donation when forming a C-H complex. Using extended Hückel calculations, Hoffmann showed that bending a square-planar 16-electron ML_4 complex leads to a high-energy filled d_{yz} orbital with π-symmetry and a low-energy empty orbital with σ-symmetry. This fragment is isolobal to CH_2 and is symmetry-allowed for insertion into C-H bonds. The Cp ring of CpML prevents relaxation and makes the transition state more accessible.

Catalytic C-H functionalization was first achieved by Eisenberg who demonstrated in 1982 that photolysis of IrH_3(CO)(dppe) under CO in benzene gave a small amount of benzaldehyde. After determining that IrH(CO)(dppe) is the active species, they showed in 1986 that Ir(PPh_3)_2(CO)Cl and Rh(PPh_3)_2(CO)Cl are catalytically active however with less than 3 turnovers. The low yield is partly due to decarbonylation of aldehyde by Rh/Ir, converting the product back to the starting materials. The Rh catalyst is more active than the Ir catalyst. Meanwhile, Tanaka found in 1987 that the more electron-rich Rh(PMe_3)_2(CO)Cl is a much more effective catalyst for alkane dehydrogenation and carbonylation. It also promotes insertion of isocyanide.

<table>
<thead>
<tr>
<th>Phosphine</th>
<th>IR absorption of CO, cm^{-1}</th>
<th>Rh concn, mM</th>
<th>yield of PhCHO, %/Rh</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMe_3</td>
<td>1970</td>
<td>7</td>
<td>1540 (147)</td>
</tr>
<tr>
<td>PBu_3</td>
<td>1955</td>
<td>7</td>
<td>398 (6)</td>
</tr>
<tr>
<td>PEt_2</td>
<td>1957</td>
<td>7</td>
<td>328 (4)</td>
</tr>
<tr>
<td>P(i-Pr)_3</td>
<td>1947</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>P(p-tolyl)_3</td>
<td>1979</td>
<td>7</td>
<td>63</td>
</tr>
<tr>
<td>PPh_3</td>
<td>1982</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>P(O(Me))_3</td>
<td>2011</td>
<td>7</td>
<td>37</td>
</tr>
</tbody>
</table>
Tanaka further showed that Rh(PMe$_3$)$_2$(CO)Cl can catalyze carbonylation of alkanes. However, Norrish type II cleavage also occurs limiting the utility of this reaction. Mechanistically, photolysis promotes CO dissociation to allow for C–H insertion. Smith reported in 1986 a ruthenium-catalyzed, phenol-directed C–H functionalization reaction. However, ethylene is the only olefin that reacts. Murai reported in 1993 that ketone can direct RuH$_2$(PPh$_3$)$_3$(CO) and Ru(PPh$_3$)$_3$(CO)$_2$ to selectively alkylate the adjacent aromatic C–H bonds. This is the first example of a practical catalytic C–H functionalization reaction. Alkenylation can also be achieved by reacting with an alkyne.
Murai later found that Rh₃(CO)₁₂ can catalyze carbonylative alkylation of imidazoles. t-Butyl aldimine, dihydrooxazine, dihydrooxazole, nitrile, and amine groups can also direct ortho-alkylation. Selective C–H functionalization can be achieved with catalyst control.

Trost showed in 1995 that the RuH₂(PPh₃)₃(CO) also catalyzes β-alkylation of cyclic enones, and ester is a better directing group than ketone. Kim also reported in 1994 that a pyridyl group can direct ortho-alkylation of arenes. Both Wilkinson's catalyst and Rh(PC₅H₃)(coe)₂Cl can catalyze this reaction. The utility of this reaction has also been expanded to alkylation of alkenes and benzylic amines.
Suggs has demonstrated in 1978 that a chelating group prevents decarbonylation of aldehyde by Rh, allowing for olefin hydroacylation. Jun reported a Ru- and 2-aminopyridine-catalyzed C–H functionalization of aldehydes in 1997. Addition of benzoic acid accelerates the reaction, and Cp₂ZrCl₂ promotes the reaction of heterocyclic aldehyde. Addition of an amine can also facilitate the reaction. Acrylates are particularly reactive due to the chelation to Rh. Allylic alcohol can be isomerized in situ to give aldehyde and used as a substrate. Additionally, in situ dehydrogenation of alcohol with excess olefin as hydrogen acceptors allows for the coupling of saturated alcohols. Wills has also demonstrated that a thioether can be used as the chelating group to prevent decarbonylation.

C–H borylation is another synthetically useful transformation. Hartwig reported in 1997 that irradiation of Cp*M(CO)$_n$BCat’ (M = Fe, Ru, or W; n = 2 or 3) in hydrocarbons give the borylated products. He then achieved catalytic C–H borylation with Cp*Re(CO)$_3$ and Cp*Rh(η$^4$-C$_6$Me$_6$). Meanwhile, Smith also showed that Ir can catalyze alkane C–H borylation. A stepwise mechanism involving a B–Ir$^V$(H)(R) intermediate was proposed.
Sames demonstrated in 2005 that Ru$_3$(CO)$_{12}$ can catalyze 2-arylation of pyridine. He further identified the active catalyst to be a dinuclear complex formed through C–H and C–P bond cleavage, cluster fragmentation, and disproportionation.

Sames also showed in 2006 that Ru$_3$(CO)$_{12}$ can also catalyze amidine-directed C(sp$^3$)–H arylation of pyrrolidine and piperidine. Interestingly, the dinuclear complexes are much less effective in this case. Amide and carbamate are much weaker directing groups.

C–H functionalization of coordinating heteroarenes using mononuclear palladium catalysts is more challenging. Sadighi first succeeded in 2004 using pyrrole-zincate as the substrate. Fagnou subsequently showed in 2005 that converting π-electron-deficient heteroarenes to N-oxides enables site-selective palladium-catalyzed directed C–H arylation. Hartwig further found that the active species for C–H insertion is a cyclometalated palladium(II) complex.
Oxidative addition of group 10 metals to C–H was first reported by Kleiman in 1963. He found that dicyclopentadienylnickel reacts with azobenzene at 135 ºC to give a C–H insertion product. Cope then showed in 1965 that reaction of potassium tetrachloroplatinate(II) with azobenzene at room temperature yielded a dimeric cycloplatination product slowly. Palladium(II) chloride reacted with azobenzene in methanol much faster and cleaner. He also demonstrated in 1968 that benzylic tertiary amine is a good directing group for C–H insertion. Benzyllic primary, homobenzylic tertiary, and bishomoallylic tertiary amines are all ineffective directing groups. Neutralization of the generated hydrogen chloride by an amine base lead to significantly increased the reaction rate. Meanwhile, Kasahara and Onoue showed that pyridine and oxime are effective directing groups.

The formation of palladacycle can be highly regioselective, favoring the formation of endo-isomer. Insertion into C(sp³)–H hybridized methyl and ethyl (but not isopropyl) groups was first demonstrated by Deeming in 1978 and later studied by Pfeffer.
Cope noted in 1965 that reaction of azobenzene palladacycle with CO gave 2-phenyl-1H-indazolone, which was confirmed by Tsuji and Heck in 1967. The insertion of isocyanide was demonstrated by Yamamoto in 1976. Pfeffer later showed that the N-coordinated palladacycles can undergo insertion with alkenes, alkynes, halogens, and acid chlorides. Holton also reported in 1981 that reaction of palladacycles with acyl chloride gave acylated products and suggested that the reaction proceeded through a Pd(IV) mechanism.

The first catalytic, directed C–H functionalization was reported by Fahey in 1970. He found that palladium chloride can catalyze chlorination of azobenzene with 24 TON.

Diamond and Mares showed in 1979 that Rh(I) salt, obtained from in situ reduction of RuCl₃, and PdCl₂ can catalyze the formation of 2-methylquinoline from aniline with 10 and 20 TON, respectively. The reaction proceeded through directed metallation, insertion of two ethylene, and dehydrogenation.

Tremont reported in 1984 that ortho-methylation of acetanilide by methyl iodide can be catalyzed by palladium acetate with 1.5 TON. Addition of AgOAc to regenerate the more electrophilic Pd(OAc)₂ from PdI₂ improved the TON to 10. Stille provided evidence in 1979 that treatment of a Pd(II) species with alkyl halide would give a Pd(IV) intermediate that undergoes rapid reductive elimination.
Moritani and Fujiwara showed in 1969 that palladium acetate can promote the direct coupling of styrene and benzene in acetic acid effectively. Addition of Cu(OAc)$_2$ or AgOAc allows for catalyst turnover by oxygen. The important role of acetate was also noted. The C–H insertion intermediate could be isolated upon addition of a dialkyl sulfide.

Fujiwara also found that addition of benzoquinone significantly improved TON presumably due to the stabilization of Pd(0) by forming a Pd(0)/BQ complex. Bäckvall reported in 1993 that acid promotes electron transfer from Pd(0) to the coordinated BQ and induces the formation of Pd(II) and hydroquinone. Acetic anhydride helps remove water and promotes the formation of tert-butyl peracetate. Fujiwara further reported an enantioselective allylic arylation in 1999.

The reaction of olefin with PdCl$_2$ to form a π-allyl species was first described by Hüttle in 1961. Na$_2$CO$_3$, NaOAc, and CuCl$_2$ facilitate the reaction, Pd(TFA)$_2$ is more reactive than PdCl$_2$, and the Cl ligand offers better complex stability. Typically, a more substituted π-allyl species is formed while steric also plays a role.

Tsuji found in 1965 that addition of a ligand such as DMSO, phosphine/phosphite, and CO activates the complex toward external nucleophilic attack by acetate, amine, or stabilized C-nucleophile. The allylic substitution reaction has been studied extensively by Trost.
Stoichiometric oxidation of allylic palladium was first reported by Hüttle in 1964. He found that oxidation of a π-allylpalladium complex with chromic acid, manganese dioxide, or palladium chloride gave enones. Jones demonstrated in 1975 that oxidation with mCPBA gives allylic alcohols.

The first palladium-catalyzed allylic oxidation was developed by Yu in 2002. He showed that oxidation of olefins by TBHP in the presence of Pd/C or Pd(OAc)$_2$/C led to the formation of enones. Further oxidation gave endiones. However, this reaction does not involve allylpalladation and proceeds through a radical pathway with the intermediacy of tert-butyl allylic peroxides.

Ishii showed in 1970 that treatment of an allylic chloropalladium species with AgOAc and CO induces the formation of allylic acetate presumably through an unstable aceto-complex. However, a catalytic variant was not known until White reported in 2004 that a combination of a sulfoxide ligand and excess benzoquinone additive allows for catalyst turnover and control of regioselectivity. She further showed in 2008 that asymmetric allylic acetoxylation can be achieved by addition of a chiral Lewis acid. Catalytic allylic C‒H alkylation with stabilized C-nucleophile was also achieved by Trost and White.
The ability of norbonene to mediate C–H insertion was first reported by Catellani in 1982. She found during the study of a multistep insertion reaction that reaction of norbonene with benzyl or phenyl bromide in the presence of a catalytic amount of Pd(PPh$_3$)$_4$ initiated a tandem process involving a benzylic or aromatic C–H insertion.

Catellani discovered in 1994 that the cis,exo-2-phenynorbornyl palladium chloride (PNP) dimer can react with alkyl iodide to release norbonene, forming the basis of the development of a catalytic reaction. Bubbling hydrogen gas through the reaction product promoted hydrogenolysis of the Pd–C bond and released the phenyl derivative.

Catellani reported the first catalytic reaction in 1997, showing that a three-component coupling reaction can be catalyzed by the PNP dimer in the presence of norbonene. She further showed in 1999 that Pd(OAc)$_2$ can be the palladium source and in 2000 that biaryls can be made by combining with Suzuki coupling. Lautens has later thoroughly explored the scope of Catellani reaction.
A general method for directed, catalytic C‒H oxidation was first reported by Sanford in 2004. She found that oxidation of the Pd(II) C‒H insertion complex lead to a Pd(IV) complex that undergoes facile reductive elimination and allows for catalyst turnover. She further obtained crystallographic support for the existence of Pd/Pt(IV) and dimeric Pt(III)-Pt(III) complexes.

Sanford found that a sp²-hybridized N-directing group promotes the palladium-catalyzed C(sp²)‒H or C(sp³)‒H functionalization efficiently. She further found that pyridine is a good ligand for palladium(II)-catalyzed direct aromatic C‒H acetoxylation without compromising aryl bromide whereas excess pyridine inhibits the reaction.

<table>
<thead>
<tr>
<th>oxidant</th>
<th>solvent</th>
<th>X</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phl(OAc)₂</td>
<td>HOAc</td>
<td>OAc</td>
<td>86%</td>
</tr>
<tr>
<td>Phl(OAc)₂</td>
<td>MeOH</td>
<td>OMe</td>
<td>95%</td>
</tr>
<tr>
<td>Phl(OAc)₂</td>
<td>EtOH</td>
<td>OEt</td>
<td>80%</td>
</tr>
<tr>
<td>Phl(OAc)₂</td>
<td>i-ProOH-HOAc</td>
<td>O'Pr</td>
<td>72%</td>
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<tr>
<td>Phl(OAc)₂</td>
<td>TFE</td>
<td>OCH₂CF₃</td>
<td>71%</td>
</tr>
<tr>
<td>NCS</td>
<td>CH₃CN</td>
<td>Cl</td>
<td>95%</td>
</tr>
<tr>
<td>NBS</td>
<td>CH₃CN</td>
<td>Br</td>
<td>93%</td>
</tr>
</tbody>
</table>

1 mol % Pd(OAc)₂, Phl(OAc)₂, HOAc
100 °C, 22 h 88% yield

5 mol % Pd(OAc)₂, Phl(OAc)₂
HOAc, Ac₂O
100 °C, 90 min 81% yield

2 mol % Pd(OAc)₂, 1.8 mol % pyridine, Phl(OAc)₂
HOAc, Ac₂O
100 °C, 5 h 70% yield, 1:2:1.3
Daugulis demonstrated in 2005 that amide is a good directing group for palladium-catalyzed ortho-arylation. Additionally, using a combination of aryl iodide as the aryl donor and silver(I) acetate is as efficient as using the hypervalent iodine(III) reagent. A halide group on the amide can also be tolerated.

Daugulis also showed in 2005 that 8-aminoquinoline amide and picolinamide are good directing groups for functionalization of C(sp³)–H groups.

Yu used a chiral oxazoline auxiliary to achieve a room temperature, palladium-catalyzed diastereoselective C–H iodination in 2005. The palladium catalyst precipitated as PdI₂ after the reaction and can be recycled in particular with addition of AgOAc. Using tert-butyl peracetate as the oxidant led to C–H oxygenation giving acetates.

Yu successfully combined directed C–H activation with Stille coupling and Suzuki coupling in 2006. Both oxazoline and pyridine can be used as the directing group. Benzoquinone is a crucial additive potentially promoting the formation trinuclear complex Cu₂Pd(OAc)₆. Methylboroxine may bridge palladium and the directing group.
The use of carboxylic acid as a weak directing group for C–H activation was first investigated by Miura in 1998. He showed that reaction of benzoic acid with acrylates can be catalyzed by a palladium/copper catalyst system to give phthalides.

Based on the observation that Miura and Rawal used Cs$_2$CO$_3$ to accelerate palladium-catalyzed, phenol-directed C–H arylation in 1997, Yu developed a method for carboxylate-directed C(sp$^2$)–H and C(sp$^3$)–H functionalization in 2007. Daugulis also reported a similar reaction in the same year.

Yu also found in 2008 that the carboxylic acid directing group can be moved one carbon away from the aromatic ring. Phenylacetic acid undergoes smooth ortho-arylation in the presence of an inorganic base. Replacement of the Ag$_2$CO$_3$ oxidant by air or O$_2$ and boronic acid/boronate with trifluoroborate significantly improve the yield and scope of the reaction.

Yu further demonstrated in 2008 that carboxylate-directed C–H functionalization can even be used to catalyze halogenation. They also found that instead of using the inorganic carboxylate salts, addition of as little as 1 equiv of DMF promoted the reaction effectively presumably due to the formation of DMF–H$^+$. Thus, halogenation of benzoic acid in DMF without inorganic base also proceeded smoothly.
Yu reasoned that unlike Rh(I) and Ir(I) complexes having low barriers for interconversion of the $\eta^1$- and $\kappa^2$-coordination, $\kappa^2$-coordination is favored for Pd(II) complexes. Addition of an inorganic base can shift the equilibrium to favor the $\eta^1$-complex and promote C‒H insertion. He has also provided support to this hypothesis through NMR and X-ray studies. He further argued that the use of a strong directing group would lead to the formation of a stable cyclopalladation intermediate that is less reactive. Weak directing groups such as carboxylate have the advantage of high reactivity toward functionalization.

Chen Orito demonstrated in 2004 that benzylic and homobenzylic amines can promote catalytic C‒H ortho-carbonylation, and Daugulis reported in 2006 a catalytic process for benzylamine- and $N$-methylbenzylamine-directed ortho-arylation. The six- and seven-membered palladcycles are less reactive than the five-membered ones. Yu introduced triflamide as another weak directing group, showing in 2008 that indoline can be prepared by triflamide-directed C‒H halogenation/cyclization.
Electron-rich substrates tend to give an even mixture of ortho, meta, and para C–H functionalization products, whereas electron-deficient substrates are not reactive. Yu showed in 2009 that sterically hindered pyridines are weak ligands that allow for the binding of electronically deficient arenes and promote selective meta-functionalization.

Yu subsequently designed an “end-on template” approach to achieve directed meta-C–H functionalization in 2012. Nitrile was used as a weak directing group here.

In 2014, Yu reported a new end-on template system for meta-selective C–H functionalization. He then reported in 2015 a Catellani-type method for meta-alkylation and arylation.
Yu discovered in 2008 various N-protected amino acids to be good ligands for promoting palladium-catalyzed C–H activation. Additionally, the corresponding chiral Pd complexes can induce asymmetric C–H cleavage with high enantioselectivity. Both carbamate and carboxylate are good weak coordinating ligands, and N–H activation (deprotonation) is important to the asymmetric induction. Using a carboxylate instead of pyridine as the directing group further improved the results. Later, Yu demonstrated that the reaction rate is increased by more than 10-fold when a N-protected amino acid ligand was used. He also found that replacing Boc with acetate improved reactivity. The more reactive ligands include Ac-Ala-OH, Ac-Val-OH, Ac-Leu-OH, and Ac-Ile-OH. Based on competition and KIE experiments, Yu proposed that the N-protected amino acid ligands shift the mechanism from electrophilic palladation to ligand-assisted proton abstraction. The weak and reversible bidentate coordination of the amino acid ligand likely plays a crucial role in facilitating the agostic interaction of between Pd and the cleaving C–H group. It may also shuttle the proton transfer to the external base.

The proton abstraction mechanism was first proposed in 1985 by Ryabov. His kinetic studies showed that palladation of N,N-dimethylbenzylamine involves a highly ordered, tight transition state. This mode of activation was refined and scrutinized by Martinez during 1994-1998. Computational studies by Sakaki in 2000 and Davies and Macgregor in 2005 suggests that the palladium center engages an agostic interaction with the cleaving C–H group instead of forming a polar Wheland arenium species. Fagnou, Maseras, and Echavarren further showed in 2006 that this concerted metallation deprotonation (CMD) mechanism is operative in various C–H functionalization reactions particular for electron-deficient substrates.
C–H functionalization has been used to build complex small molecules for decades. Trost reported in 1979 an asymmetric synthesis of ibogamine featuring a palladium-mediated cyclization reaction. Deuterium-labeling experiment indicated that the reaction proceeded through a C–H functionalization mechanism.

Bringmann used a palladium-catalyzed intramolecular C–H arylation reaction to establish the biaryl bond of ancistrocladine in 1986 based on the dehydrohalogenation reaction developed by Ames in 1983. With remote chiral centers, the cyclization occurred with surprisingly good diastereoselectivity. Later, this approach was used by O.R. Martin and K. Suzuki to achieve the synthesis of gilvocarcins in 1990 and 1992, respectively.

Boger also reported in 1988 a palladium-mediated cyclization reaction for the synthesis of polypyrrole natural product prodigiosin. This method is based upon the dehydrogenative biaryl coupling developed by Itahara in 1980. Boger found that using a substoichiometric amount of soluble Pd(OAc)$_2$ in acetic acid or Pd(TFA)$_2$ in trifluoroacetic acid promoted this reaction with 1 TON, but increasing the amount of palladium led to coupling of the product. The problem could be solved by using polystyrene-supported palladium acetate.

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Advanced Synthesis and Catalysis — C–H Activation

Chen
Holton showed in 1977 that a methylthiomethyl (MTM) ether group can be used as a strong directing group to change the regioselectivity of C‒H insertion. Additionally, depalladation of the palladacycles can be achieved by reduction or reacting with enone to give a coupling product.

Holton further used this directed C‒H functionalization method to complete the synthesis of Narwedine in 1988. First, a MTM-directed C‒H insertion gave a pincer complex as a 1:1 mixture of S-diastereomers in nearly quantitative yield. Next, oxidation of the phenol group with thalic trifluoroacetate provided a demethylated phenolic coupling product. Warming the reaction to room temperature induce a rearrangement reaction followed by depalladation and loss of the MTM group to yield narwedine.
Sames reported in 2000 a synthesis of rhazinilam using a C–H platinum-mediated dehydrogenation reaction to functionalize one of the two geminal ethyl groups on a pyrrole-fused six-membered ring. Reaction of a pyridine-bearing imine with a dimethyl platinum complex led to the formation of a cationic platinum complex. Further treatment of this complex with triflic acid yielded a new complex with a loss of a methane molecule. Subsequent heating in trifluoroethanol provided a platinum hydride species from C–H insertion and β-hydride elimination. He later replaced the pyridine with a chiral oxazoline group and accomplished the asymmetric synthesis of rhazinilam.

Trauner also reported in 2005 a concise synthesis of rhazinilam using a different C–H functionalization strategy. The arylation of electron-deficient pyrrole proceeded with good efficiency to give the critical nine-member ring system. Hydrolytic removal of the protecting group on the amide furnished rhazinilam.

Gaunt developed another C–H functionalization approach to synthesize rhazinilam in 2008. He previously showed that the regioselectivity of functionalization of pyrrole can be controlled by the N-protecting group. The C2-functionalized product is preferred with an electron-withdrawing N-protecting group and the C3-functionalization is favored with a sterically hindered group. This method allows for an easy setup of the all-carbon quaternary center.
Sames reported in 2002 an elegant strategy to construct the teleocidin B4 core by sequential functionalization of a tert-butyl group. This work clearly demonstrate the power and potential of C–H functionalization in total synthesis.

The strategy of palladium-mediated C–H functionalization of indole has also been used by Corey to synthesize austamide alkaloids and okaramine N in 2003 and 2004, respectively.

Stoltz reported in 2004 the application of C–H functionalization of pyrrole to accomplish the synthesis of dragmacidin F. Itami achieved the synthesis of dragmacidin D using three different C–H arylation reactions.
Gauthier, Jr. at Merck reported in 2005 a highly efficient C–H arylation reaction that enabled the synthesis of an $\alpha_{2/3}$-selective GABA agonist. Direct arylation of imidazotriazine proceeded smoothly at 1 mol % catalyst loading.

Bergman and Ellman developed a rhodium-catalyzed, imine-directed C–H functionalization reaction in 2003 and applied it to the synthesis of lithospermic acid in 2005. Using a ferrocene-derived phosphine ligand gave the cis-isomer as the only diastereomeric product.

Yu also achieved the stereoselective synthesis of lithospermic acid in 2001 with two C–H functionalization reactions. First, a rhodium-catalyzed C–H insertion using Davies’s chiral catalyst and Fukuyama’s chiral auxiliary set up the core skeleton with good stereoselectivity. Next, after hydrolyzing off the chiral auxiliary, the resulting acid group was used as the directing group to promote C–H olefination. An $N$-protected amino acid was used as the ligand to facilitate this palladium-catalyzed reaction.