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Direct activation of relatively unstrained carbon–carbon bonds in homogeneous systems

Alpay Dermenci[a], **Jotham W. Coe**[a], and **Guangbin Dong**[b]

[a]Pfizer Inc., Worldwide Medicinal Chemistry, Eastern Point Rd., Groton, CT 06340, USA

[b]Department of Chemistry and Biochemistry, University of Texas at Austin, 1 University Station A5300, Austin, TX 78712-0165, USA

Abstract

New modes of chemical reactivity are of high value to synthetic organic chemistry. In this vein, carbon–carbon (C–C) activation is an emerging field that offers new possibilities for synthesizing valuable complex molecules. This review discusses the pioneering stoichiometric discoveries in this field up to the most recent synthetic applications that apply catalytic transformations. Specifically, the review focuses on C–C activation in relatively unstrained systems, including stoichiometric reactions, chelation-directed and chelation-free catalytic reactions. While the field of C–C activation of relatively unstrained systems is underdeveloped, we expect that this review will provide insight into new developments and pave the path for robust, practical applications.

New modes of catalytic chemical reactivity can provide powerful transformations for synthetic chemists to attain higher efficiency and more direct routes to desired molecules. Two areas of research that fit the criteria for novel mechanisms and transformations include carbon–hydrogen (C–H) and carbon–carbon (C–C) activation. While catalytic C–H activation has garnered significant recent attention by the synthetic community, reports of C–C activation methods are less prominent in the literature. C–C Activation is often viewed as a destructive mode of reactivity, counter to the primary focus on developing methods to *form* C–C bonds rather than to *break* them. This review will show how selective functionalization of the metal center in conjunction with C–C activation can lead to unique methods for constructive bond formation.

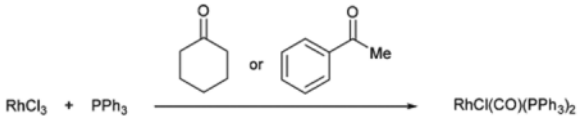
When compared to C–H activation, C–C activation is kinetically challenging. C–H bonds are typically more abundant and C–C bonds are hindered. Therefore, C–H bonds more readily display proper orbital overlap trajectories with the metal center than C–C bonds. Thermodynamics play less of a role as C–C oxidative addition can in fact be exothermic, although cleavage of C–C bonds can also be thermodynamically uphill. Methods for transition-metal-mediated C–C activation employ strategies mainly involving strain-release, aromatization, and chelation-assistance (proximity effect) to overcome these barriers. The latter two have proven useful for the activation of unstrained C–C bonds, which remain particularly challenging in the context of C–C activation of unstrained C–C bonds.

Correspondence to: Jotham W. Coe; Guangbin Dong.

This review primarily focuses on the direct activation of C–C bonds in relatively unstrained systems, *i.e.* non-three or four-membered ring systems. While not intended to comprehensively cover all literature references, it rather provides a perspective on the scope of reactivity through selected examples to highlight representative reactions types. Chronological order is roughly followed to loosely track the progress of research for the activation of unstrained C–C bonds. Three main sections will be discussed: (1) stoichiometric C–C activation reactions, (2) chelation-directed catalytic C–C activation reactions and (3) chelation-free catalytic C–C activation reactions. Olefin metathesis, retro-aldol reactions, β-carbon elimination reactions, C–CN activation,[1] decarboxylation,[2] deallylation,[3] solid-state photochemical[4] reactions, diazoalkane-carbonyl homologation,[1] Baeyer–Villiger oxidation and other oxidative C–C cleavage reactions, while all involving C–C bond breaking or rearrangement, will not be discussed here as these topics are either beyond the scope of the review or have been thoroughly reviewed elsewhere.[5]

Stoichiometric reactions

One of the first examples of C–C activation in an unstrained system was reported by Rusina and co-workers in 1965.[6] They observed that when $RhCl_3$ and PPh_3 were heated in a number of different alcoholic solvents, they obtained golden-yellow crystals of $Rh^{I}Cl(CO)(PPh_3)_2$. The same complex was isolated when conducted in cyclohexanone and acetophenone at reflux. Although no mechanism was proposed, it is likely that $Rh^{I}Cl$-$(CO)(PPh_3)_2$ formation is the result of a C–C activation event. Furthermore, they suggest that elevated temperatures were required as no complex was formed when the reaction was conducted in acetone (b.p. 57 °C).



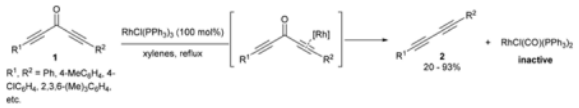
(1)

A few years after the work of Rusina, Müller and coworkers[7,8] showed that Wilkinson's complex $RhCl(PPh_3)_3$ can cleave the sp–sp^2 bonds of diynones (**1**), resulting in decarbonylation and reductive elimination to produce diynes (**2**) and $RhCl(CO)(PPh_3)_2$ (eqn (2)). A stoichiometric amount of RhCl-$(PPh_3)_3$ was required for full conversion as the RhCl(CO)-$(PPh_3)_2$ carbonyl byproduct does not catalyze the reaction. This method was demonstrated to work on a number of different symmetrical and unsymmetrical diynones with varying electronic and sterics properties to produce the corresponding diynes (20–93%). In one example, a monoynone produced a disubstituted alkyne in 8% yield. A mechanistic discussion in the catalytic version of this reaction will be presented in a later section of this review.

Wilkinson's complex effectively decarbonylates unstrained 1,2- and 1,3-diketones (**3**), as shown by Teranishi and coworkers[9] who observed monoketone products (**4**) under refluxing toluene (eqn (3)). They reported the isolation of an acetylacetonato complex, which proved

inactive as a catalyst. However, the Rh-carbonyl complex isolated from the reaction was found to be active in the decarbonylation of acetylacetone to provide methyl ethyl ketone. Their studies highlighted specificity of Rh in the decarbonylation of 1,2- and 1,3 diketones as other catalysts, such as $RhCl_3–3H_2O$, $IrCl_3–3H_2O$, $PdCl_2$, and $CoCl_2–6H_2O$, were screened but failed to promote decarbonylation chemistry.

In 1971, King and co-workers showed that 5-acetyl-1,2,3,4,5-pentamethylcyclopentadiene (**5**) undergoes C–C bond cleavage when treated with $Co_2(CO)_8$ in cyclohexane at 110 °C for 22 h to form stable complex **6** (eqn (4)). Eilbracht and Dahler[10] later demonstrated that alkyl substituents can also participate in C–C activation *via* aromatization. Diene **7** reacts with $Fe_2(CO)_9$ to form a stable complex (**8**), which when heated with additional $Fe_2(CO)_9$ in benzene at 80 °C provides a cyclic Fe species **9**. Furthermore, Crabtree and co-workers[11] also showed that iridium complexes can form Cp-complex *via* C–C bond cleavage in various gem-dialkyldienes (eqn (6)). Initially, $[IrH_2(Me_2CO)_2((p\text{-}FC_6H_4)_3P)_2]$ underwent dehydrogenation with compound **10** to form diene complex **11**, and demethylation *via* C–C activation provided complex **12**. While not all examples of aromatization strategies for C–C activation are covered here,[12] these examples demonstrate that aromatization can drive C–C activation with a variety of different metals and substrates.



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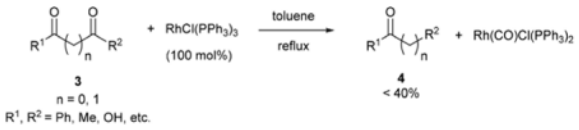

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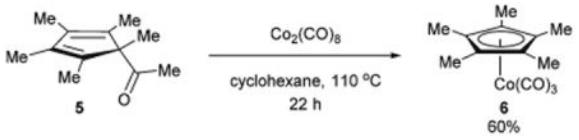

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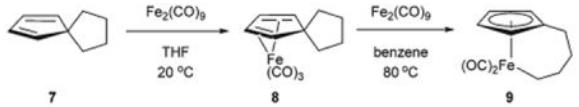

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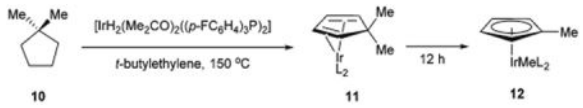
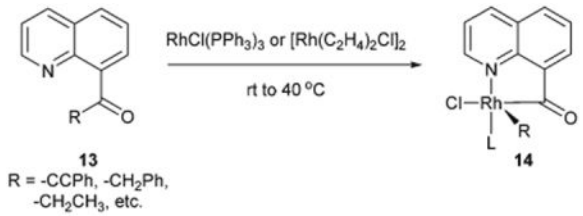


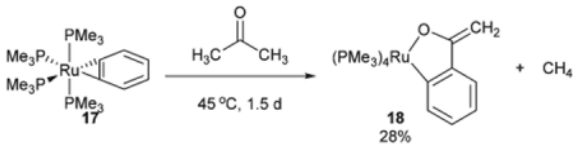
(6)

Chelation-assisted activation of α C–C bonds to a carbonyl group was first demonstrated by Suggs and co-workers[13] through insertion of Rh into a series of quinoline-derived substrates under mild conditions (rt to 40 °C) (**13**, eqn (7)). This strategy was found applicable for the activation of alkynyl and alkyl ketones; however, styryl ketones did not react even at high temperature. Deuterium labeling studies showed that in this case C–H activation of the alkyl substituents did not occur prior to C–C activation. Furthermore, this approach was used to synthesize chiral rhodium alkyl species through the incorporation of an α chiral substituent (**15**, Scheme 1). When the chiral metal-complex **16** was treated with $P(OMe)_3$, reductive elimination returned the starting material with no loss of optical purity. Given that reductive elimination typically occurs with retention of configuration[14] C–C activation must also occur through retention of configuration. The authors proposed that the reaction followed a mechanism similar to the Baeyer-Villiger reaction through a tetrahedral intermediate.



(7)

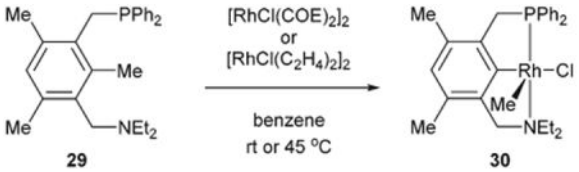
In 1989 Bergman and co-workers[15] reported the synthesis of a highly reactive Ru benzyne complex **17** that was able to active C–H, C–N, N–H, O–H and C–C bonds under relatively mild conditions.[16] When the catalyst is heated with acetone at 45 °C for 1.5 days, Ru complex **18** was obtained in 28% isolated yield and ^{1}H NMR analysis identified methane as a byproduct (eqn (8)). Bergman later identified a hydroxyruthe-nium complex **19**, also capable of promoting C–C activation under mild conditions. When hexafluoroacetone was treated with **19** in benzene at room temperature for 1 h, complex **20** was formed along with an equivalent of fluoroform. By the mechanism shown in Scheme 2, dissociation of hydroxide permits reversible formation of cationic complex **21**, allowing the substrate to bind giving intermediate **22**. Hydroxide ion attack on the carbonyl forms species **23**, which undergoes C–C cleavage to produce fluoroform and complex **20**.



(8)

In 1992[17] and subsequent papers[18] in following years, Rosenthal and co-workers reported that titanium and zirconium could be used to activate the internal C–C bond of diynes (24, Scheme 3). A general scheme is provided to illustrate the basic mechanism of this reaction. Most characteristic to the mechanism is that the reaction goes through a metallocyclocumulene to give the observed dimeric products (**25**). Crystallographic data was obtained to support the proposal of this mechanism. This work demonstrates that early transition metals are also capable of C–C bond activation.

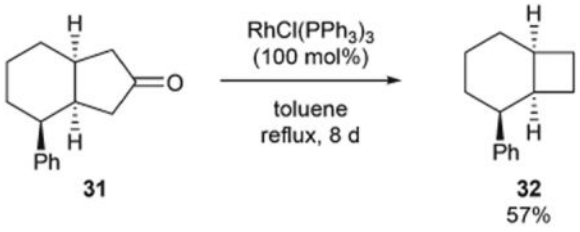
The activation of strong unstrained C–C bonds was demonstrated by Milstein and co-workers[19] with pincer complexes. When bisphosphine **26** was reacted with $HRh(PPh_3)_3$ at room temperature in THF, a thermally stable C–H activation product was obtained in quantitative yield (**27**, Scheme 4). When this complex was heated at 90 °C in the presence of H_2, the C–C activation product (**28**) was formed quantitatively. The mechanism of C–C activation likely involves reversible C–H activation followed by subsequent C–C activation. These results suggest that the C–C activation and formation of a strong Rh–Ar bond is thermodynamically more favorable than C–H activation. Milstein and co-workers[20,21] indicated that the C–C activation event proceeds through a three-centered mechanism rather than an η^2-arene complex suggesting that the metal center is perfectly positioned for direct C–C activation. Mil-stein and co-workers[22] also studied an unsymmetrical pincer ligand bearing a phosphine and amine chelate (**29**). C–C Activation occurs exclusively (eqn (9)) under mild conditions (rt to 45 °C) to provide complex **30** with no evidence for C–H activation or initial complexation of Rh to the ligand. This observation may be explained by the less sterically demanding amine ligand with its hard electronic influence versus a soft phosphine promoting rapid reversible C–H activation. These experiments demonstrate the feasibility of activating unstrained C–C bonds, and support the notion that the cleavage can be favored from both kinetic and thermodynamic respects under the correct circumstances.



(9)

In 1994, Ito and co-workers showed that Rh-catalyzed C–C activation can take place with strain-free cycloalkanones to provide strained ring-contracted products.[23] Cyclopentanone

derivative **31** was decarbonylated using an equimolar amount of Wilkinson's catalyst to provide a strained cyclobutane (**32**) in 57% yield after refluxing for 8 days (eqn (10)). Larger rings, such as cyclododecanone, were decarbonylated after heating at higher temperature (150 °C) for 3 d to provide an eleven-membered carbocycle, albeit in much lower yield (20%, eqn (11)).



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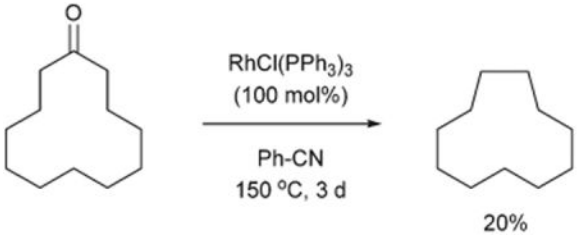
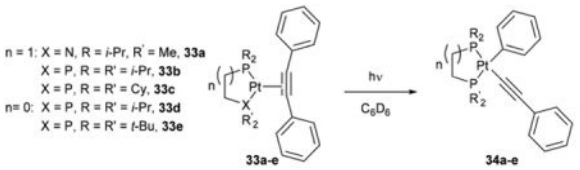


(11)

Jones and co-workers[24] presented a unique case where Pt can cleave the sp^2–sp C–C bonds of diphenyl acetylene under photochemical conditions.[25] Shedding UV light onto a series of air- and moisture-sensitive Pt-η^2-alkyne-complexes (**33a**–**e**) afforded unsymmetrical Pt^{II} complexes **34a**–**e** with a phenyl group σ-bonded to the metal center (eqn (12)). The structures were confirmed by single crystal X-ray diffraction, and ^{1}H NMR analysis shows platinum satellites for a single set of *ortho*-phenyl protons indicating that the phenyl group is indeed σ-bonded to the Pt center. Interestingly, when specific complexes **34b** and **34e** were thermally activated, a reductive elimination took place to reform the Pt-η^2-alkyne complexes (**33b** and **33e**, eqn (13)). The reversible nature of the reaction under thermal conditions suggests that oxidative cleavage of sp^2–sp C–C bonds in these particular complexes is thermodynamically uphill.[26]



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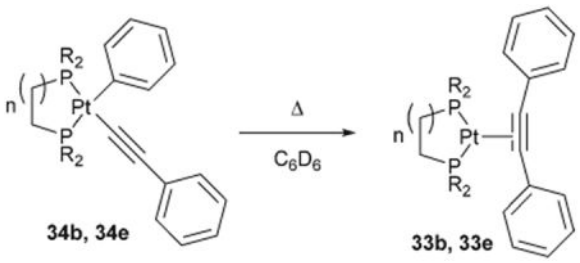
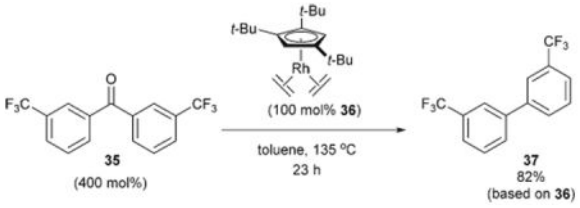


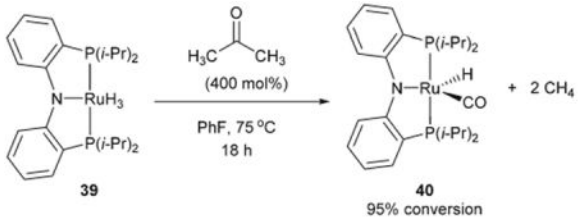
(13)

In 2004, Daugulis and Brookhart[27] reported the use of a Rh complex capable of decarbonylation. For example, 3,3′-bis(tri-fluoromethyl) benzophenone (**35**) was decarbonylated with Cp*Rh(C_2H_4)$_2$ (**36**) in refluxing toluene to give biaryl product **37** in 82% yield (based on catalyst, eqn (14)). Catalyst **36** was also found to successfully decarbonylate chalcone. Heating chalcone with Cp*Rh(C_2H_4)$_2$ at 120 °C forms complex **38**, however upon further heating at elevated temperatures (150 °C) decarbonylation occurs to form stilbene in 36% yield (Scheme 5). A number of other benzophenones and aceto-phenones were decarbonylated and while electronic factors did not influence the rate of decarbonylation with benzophenones, more electron-withdrawing substituents (*e.g.* CF_3) on aceto-phenones gave substantially faster reaction rates.



(14)

Following the work of Daugulis and Brookhart, Ozerov and co-workers[28] presented an electron-rich pincer-ligated Ru complex (PNP)(Ru)H_3, **39**) that can successfully decarbonylate acetone. Heating of acetone (4 equiv.) with **39** in fluorobenzene at 75 °C for 18 h resulted in the decarbonylation of acetone to form **40** in 95% conversion (eqn (15)). The proposed mechanism is shown in Scheme 6, where **39** cleaves a single α C–C bond of acetone to provide ruthenium-acyl complex **41**. Reductive elimination produces an equivalent of methane (observed by ^{1}H NMR) and complex **42**, which can react with hydrogen to extrude another equivalent of methane and result in the formation of complex **40**. Ozerov and co-workers conducted DFT studies, in addition to ^{1}H NMR experiments, to support the mechanistic rationale and the exothermic nature of the reaction (−51.5 kcal mol^{-1}). They proposed two main thermodynamic driving forces for the reaction. The first involves the favorable binding of CO over H_2 by 38.9 kcal mol^{-1} to the metal center. The second is preferable formation of C–H bonds over C–C bonds by 19.9 kcal mol^{-1}, supporting the production of two equivalents of CH_4 rather than one equivalent of C_2H_6.

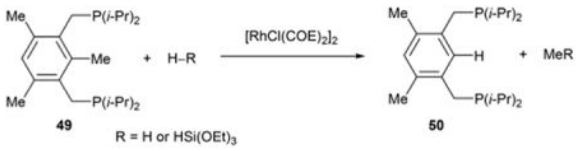


(15)

Another form of chelate-assisted C–C activation was reported by Ruhland and co-workers showing that sp^2–sp^2 C–C bonds in biaryls and benzophenones can be successfully cleaved with phosphonite directing groups.[29] For instance, when biaryl compound **43** was treated with $Ni(PPh_3)_2(CO)_2$ at room temperature, the two phosphinite groups coordinated to the metal center and extruded two equivalents of PPh_3 to provide complex **44** (Scheme 7). Upon heating of **44** under 5 bar CO, benzophenone complex **45** was afforded *via* C–C activation and CO insertion The reverse reaction was also shown to be possible in the absence of CO, where ligand **46** was treated with $Ni(PPh_3)_2(CO)_2$ to afford complex **45** and upon heating (95 °C) decarbonylation occurred to give complex **44** (20%, 4 days). Decarbonylation was also observed when **46** was treated with $Ni(COD)_2$, to give a 4 : 1 mixture of complexes **47a** and **47b**, respectively (Scheme 8). The formation of **47a** and **47b** arises from two degenerate intermediates **48a** and **48b**, which are in equilibrium as observed by NMR analysis. Extensive experimentation and further NMR analysis provided a mechanistic understanding of the carbonylation and decarbonylation reactions. In the case of carbonylation reaction, they proposed that CO dissociation occurred prior to C–C activation, whereas in the decarbonylation pathway CO deinsertion occurred after electron-rich Ni(0) oxidatively inserted into the C–C bond. Similar C–C activation of benzophenone derivatives was observed by Obenhuber and Ruhland with other transition metals such as Ir (*e.g.* Vaska complex)[30] and Rh (*e.g.* $[Rh\text{-}(COE)_2Cl]_2$).[31]

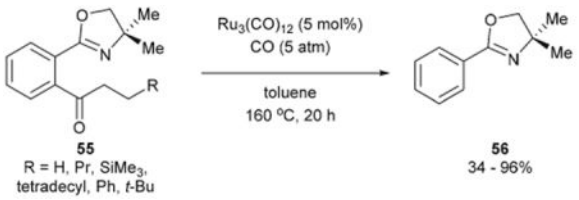
Catalytic chelation-directed C–C activation of unstrained substrates

In 1998, Milstein and co-workers[32] described a catalytic version of the C–C activation with their bidentate phosphine substrates in converting **49** to **50** under H_2 pressure or with excess $HSi(OEt)_3$ (eqn (16)). Although not optimized at the time, $[RhCl(COE)_2]_2$ showed 100 turnovers with H_2. The proposed catalytic cycle is shown in Scheme 9. The first step involves hydrogenation of the COE ligand and complexation to the bidentate substrate to form **51**. At this stage C–C activation can ensue to achieve Rh^{III} intermediate **52**, at which point hydrogenolysis of the Rh–methyl bond produces methane and complex **53**. Reductive elimination results in Rh^{I} **54**, which can undergo exchange with the substrate to produce **50** and allow Rh^{I} to reenter the catalytic cycle.



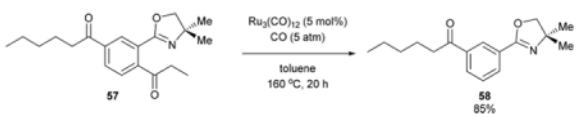
(16)

A year after Milstein's report on catalytic C–C activation, Murai and co-workers reported a chelation-assisted decarbonylation reaction *via* activation of unstrained C–C bonds.[33] They reported the use of $Ru_3(CO)_{12}$ (5 mol%) under 5 atm CO in toluene at 160 °C to undergo oxazoline-directed decarbonylative C–C cleavage of alkyl phenyl ketones (**55**) to the corresponding products in 34–96% yield (**56**, eqn (17)). They also demonstrated that the directing group is necessary, as in substrate **57** decarbonylation only occurred *ortho* to the directing group to furnish **58** in 85% yield (eqn (18)).



(17)

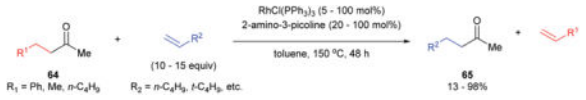
Murai and co-workers propose two possible mechanistic pathways that lead to the observed product (Scheme 10). Coordination of Ru to the starting material (**55**) followed by nucleophilic attack at the carbonyl provides complex **59**. At this point there are two possible C–C bonds that can be cleaved, the Ar–CO C–C bond or the CO–alkyl C–C bond. Cleavage through pathway A would lead to six-membered rhodacycle **60**, which after decarbonylation (to give **61**) and β-hydride elimination would provide the desired product. Alternatively, pathway B would provide the five-membered rhodacycle **62**, which can undergo decarbonylation to provide the same intermediate (**61**) or it can first undergo β-hydride elimination to give complex **63**, which would release a molecule of ketene and reductively eliminate to give the desired product. Murai and co-workers suggest that pathway B is more plausible. Benzyl ketone derived substrate (R = Ph) was reacted in methanol to give 73% yield of the desired product (**56**) isolated along with 34% of methyl phenylacetate through methanolysis of intermediate **62** or trapping of phenyl ketene.



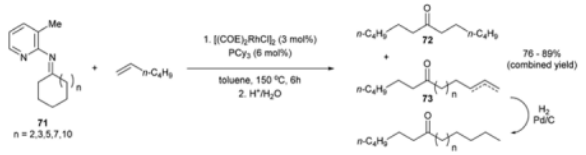
(18)

In the same year, Jun and co-workers[34] reported a catalytic C–C activation of unstrained ketones using 2-amino-3-picoline as a cofactor.[35] As shown in eqn (19), Wilkinson's catalyst and 2-amino-3-picoline promote C–C activation and alkyl group transfer in the presence of ketones (**64**) and terminal olefins with good yields overall (42–98%). Internal olefins typically did not work as well giving lower yields. The proposed mechanism of the reaction explains the preferred C–C cleavage on the homobenzyl side of the ketone (Scheme 11). The first step of the reaction involves condensation of 2-amino-3-picoline to provide imine **66** and H_2O. Coordination of Rh(I) to the substrate followed by C–C activation gives rhodacycle **67**, which can undergo β-hydride elimination, possible only on the homobenzylic side, to form an equivalent of styrene and complex **68**. Migratory insertion into 1-hexene affords intermediate **69**, which after reductive elimination provides ketimine **70** and regenerates the Rh(I) catalyst. Hydrolysis of ketimine **70** provided product **65** and 2-amino-3-picoline which can reenter the catalytic cycle. This process was also demonstrated with the C–C activation of secondary alcohols, where alkyl-group-exchange takes place after initial oxidation of the secondary alcohol to the ketone *via* transfer hydrogenation.[36]

Jun and co-workers further developed a picoline-directed C–C activation strategy for ring-opening and skeletal rearrangement of several different cycloalkanone imines.[37] For example, when cycloalkanoketimine **71** is subjected to $[(COE)_2RhCl]_2$ (3 mol%) and PCy_3 (6 mol%) in toluene at 150 °C for 6 h a mixture of symmetrical and unsymmetrical ring-opened products (**72** and **73**, respectively) were obtained in good yields (76–89%, eqn (20)). Smaller ring systems such as cyclopentanoketimine and cyclohexanoketimine reacted poorly and gave yields of less than 10%. The mechanism of this reaction (Scheme 12) is similar to that of the previously discussed reaction, where 2-amino-3-picoline directs Rh(I) to cleave the α C–C bond of the ketimine providing intermediate **74**. β-Hydride elimination gives Rh–H **75**, which can then add across an equivalent of 1-hexene to provide complex **78**. Hydrolysis of **78** gives product **73**; alternatively, **78** can undergo another cycle of alkyl-group transfer to give the symmetrical ketimine **79**, ultimately leading to ketone **72**.



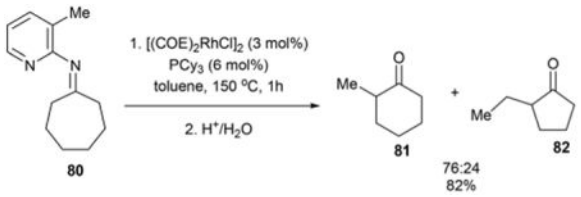
(19)



(20)

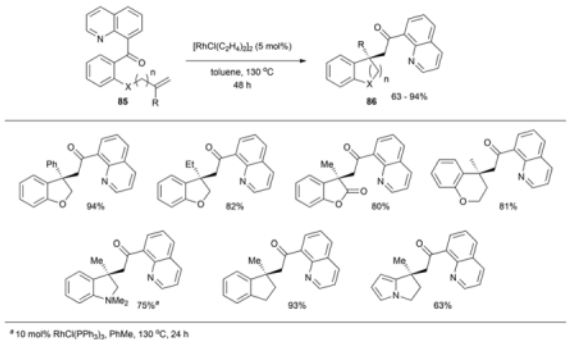
When the reaction with seven-membered ketimine **80** was run without 1-hexene, a rearrangement occurred followed by hydrolysis to produce cyclohexanone **81** and

cyclopentanone **82** in 82% yield with 76 : 24 ratio, respectively. Other rings sizes gave lower yields (0–21%). The mechanism of this rearrangement follows a similar sequence as that in Scheme 12. For example, rather than addition to 1-hexene, the Rh^{III} intermediate **75** reinserts into the appended olefin in a 6-*exo* fashion to give an intermediate that can reductively eliminate to provide cyclohexanone product **81**. On the other hand, for product **82**, after reinsertion of the appending olefin, a second β-hydride elimination (alkene chain-walk) followed by another addition across the olefin and reductive elimination would result in cyclopentanone **82**. Jun and co-workers also showed that when bicyclic systems such as bicycle[3.2.1]octan-2-one **83** were subjected to the reaction conditions, a 5,5-fused bicyclic ketone **84** is obtained in 25% yield following the mechanism proposed below (Scheme 13).



(21)

In 2009, Douglas and Dreis[38] reported an intramolecular carboacylation reaction. Quinolines were utilized as directing groups for catalytic C–C σ bond activation with Rh. Refluxing substrate **85** with 5 mol% $[RhCl(C_2H_4)_2]_2$ in toluene effectively results in all-carbon quaternary stereocenter-containing compound **86** in moderate to excellent yields (63–94%, eqn (22)). A number of different substrates with various linkers participate. An intermolecular version of this transformation was reported later that year by the same group on insertion of norbornene-type alkenes.[39,40]

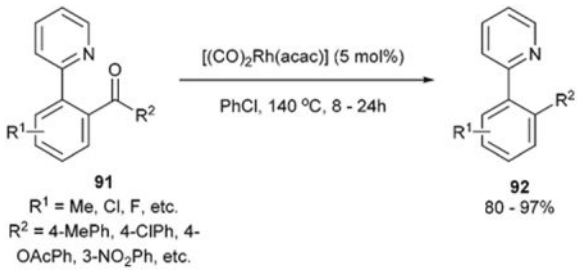


(22)

Johnson and co-workers published mechanistic studies regarding the catalytic cycle for these transformations (Scheme 14).[41] They found slightly different mechanistic pathways by investigating the use of $RhCl(PPh_3)_3$ and $[RhCl\text{-}(C_2H_4)_2]_2$ as catalysts, respectively. With $RhCl(PPh_3)_3$ the proposed catalytic cycle is shown in Scheme 13, wherein the reaction was

found to be zero-order in substrate and first-order in catalyst, and the C–C activation step was determined to be rate-limiting. The resting state of the reaction is when catalyst is bound to the substrate in complex **87**. Next, C–C activation and acylation of the metal center provides intermediate **88**, which rearranges to the quaternary center in complex **89**. Reductive elimination would then produce **90**, where the product can be exchanged with another equivalent of substrate allowing the catalyst to reenter the catalytic cycle. PPh_3 may also intercept **90** to free the catalyst. On the other hand, when the reaction was studied for $[RhCl(C_2H_4)_2]_2$ a slightly different catalytic cycle was proposed. The reaction is second-order overall, first-order in both substrate and catalyst, suggesting that the resting state of the catalyst is when it is not bound to either substrate or product. The rate-limiting step was determined to be C–C activation with 1,1′-disubstituted alkenes or substrates with longer linkers influencing the reaction rate. The main intermediates of catalytic cycle for $[RhCl(C_2H_4)_2]_2$ are similar to $RhCl(PPh_3)_3$, with the exception of the resting state of the catalyst.

In 2012, Shi and co-workers[42,43] published a pyridine-directed C–C activation strategy for the decarbonylation of biaryl ketones and alkyl/alkenyl aryl ketones (**91**). The optimized conditions employ 5 mol% $[(CO)_2Rh(acac)]$ in refluxing chlorobenzene to provide the decarbonylated products (**92**) in 80–97% yield (eqn (23)). A number of different aryl, alkyl, and alkenyl groups participate under the reaction conditions and both electron-donating and electron-withdrawing groups afforded good yields. Nitrogen-based directing groups other than pyridine (*e.g.* pyrazolyl and oxazolyl) provided decarbonylation products in lower yields (52 and 44%, respectively). The proposed mechanism for the decarbonylation is shown in Scheme 15. The reaction is initiated by coordination and subsequent oxidative addition to form either intermediate **93** or **94**, and decarbonylation forms **95** followed by reductive elimination giving the observed product. Shi and co-workers propose the five-membered rhodacycle (**93**) as the favored pathway, although the other pathway cannot be ruled out. The reaction was not promoted by photoirradiation (as the reaction takes place in the dark).



91
R^1 = Me, Cl, F, etc.
R^2 = 4-MePh, 4-ClPh, 4-OAcPh, 3-NO_2Ph, etc.

92
80 - 97%

(23)

Catalytic C–C activation without chelation

Fillion and co-workers[44] showed that unstrained C–C σ bonds in benzylic Meldrum's acid derivatives (**96**) could be hydrogenolyzed to produce various benzylic products **97** (eqn

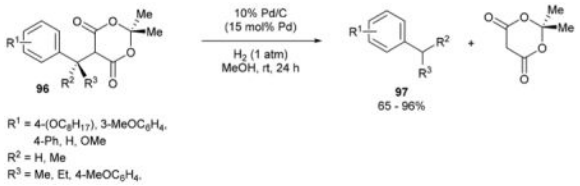
(24)). When subjected to 15 mol% of 10% Pd/C under 1 atm of H_2 for 24 h in MeOH at room temperature, benzylic products were obtained in good to excellent yields (65–96%). Electronic effects were observed on the phenyl moiety. *meta*-Substituted substrates (OC_8H_{17}) gave no product whereas the *ortho*- and *para*-substituted analogs gave facile hydrogenolysis and high yields. At the benzylic position, sterics played an important factor such that incorporation of an i-Pr group hampered the reactivity giving only modest conversion; whereas methyl substitution gave near full conversion and high yields. When enantioenriched substrates were hydrogenolyzed, an inversion of stereochemistry is observed with only slight erosion of the enantiomeric ratio. Furthermore, deuterium labeling studies showed that full incorporation of deuterium was observed only when both the solvent and gas were labeled and only partial incorporation was observed when run separately. Therefore, it is likely that the reaction follows an S_N2 type mechanism that involves nucleophilic attack by palladium to obtain a benzylic organopalladium intermediate, which undergoes protonation by methanol.

In 2012, Arisawa, Yamaguchi and co-workers[45] reported a method for preparing unsymmetrical ketones through a Rh-catalyzed acyl-transfer reaction that requires no chelation assistance. Under optimized conditions $RhH(CO)(PPh_3)_3$ with 1,2-bis(diphenylphosphino)benzene (dppBz) in *N,N*′-dimethyl-imidazolidinone (DMI) at 150 °C for 12 h results in the transfer of acyl groups between a variety of benzyl ketones (**98**) and thioesters/aryl esters (**99**) to provide the respective products **100** and **101**. In general, a combination of different substrates gave good yields with the exception of 1,2-diphenylethanone, which gave 21% yield of unsymmetrical benzyl ketone and 18% yield of the thioester. The reaction was also applied to the acyl transfer of benzyl ketones (**102**) with aryl esters (**103**) and gave modest to good yields (39–71%) of the benzyl ketone and thioester. Multiple equivalents of the starting thioester favor the forward direction in this equilibrium driven reaction. While the exact mechanism is still unclear, the authors propose that the reaction first undergoes CO–benzyl bond cleavage by a low-valent Rh, followed by exchange with the thioester and reductive elimination to give the product.

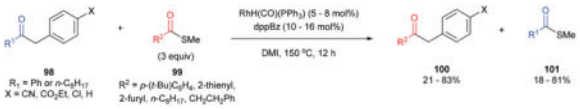
In 2013, Dong and co-workers[46] reported a catalytic version of the Rh-mediated decarbonylation of diynones initially reported by Muller. The key factor for promoting this catalytic process was a bidentate phosphine ligand, which is believed to assist in CO elimination from the metal center allowing regeneration of the active catalyst. The reaction works well for a number of symmetrical and unsymmetrical diynones **106** using 2.5 mol% $[Rh(COD)Cl]_2$ and 6 mol% 1,1′-bis(diphenyl-phosphino)ferrocene (dppf) in refluxing chlorobenzene to obtain the diyne products **107** (21–91%). The reaction is amenable to substrates that present both electronic and steric variations. This method has been used for natural product modification (eqn (28)). It was also applied to the synthesis of a highly conjugated ynediyne **108** through a decarbonylation followed by Sonagashira coupling, in which the orthogonality of this process to other Pd and Cu-catalyzed methods (*i.e.* tolerance of aryl halides) was demonstrated, making it a complimentary strategy (Scheme 16).

The proposed mechanism for the decarbonylation is illustrated in Scheme 17. The first step involves coordination of the substrate to the metal center (**109**), bringing the metal into close proximity for C–C bond cleavage. Oxidative addition of Rh^I gives Rh^{III}-complex **110**, which

undergoes decarbonylation and CO migration to form complex **111**. Rapid reductive elimination provides the product and Rh carbonyl complex, which is regenerated into its active form through ligand-assisted release of CO upon substrate binding. The first three steps are in principle all reversible. Also, in the case of unsymmetrical diynones, only unsymmetrical diynes are obtained, suggesting that the reaction is strictly intramolecular without observed intermolecular exchange of acetylene units.



(24)



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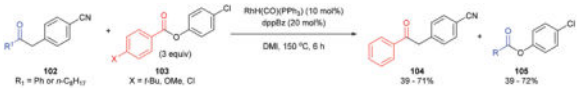

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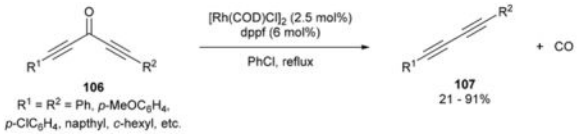
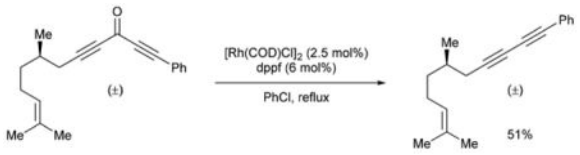
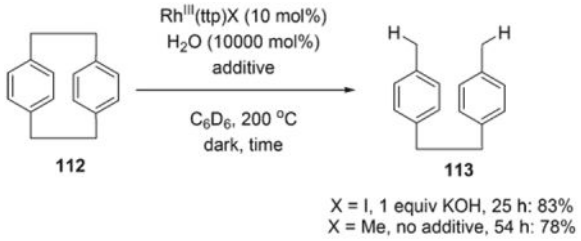


(27)



(28)

Chan and co-workers have developed a rhodium phorphyrin for the catalytic C–C activation of aliphatic [2.2]paracyclophane (**112**, PCP).[47] Similar chemistry was developed by the group previously in the context of C–C activation using stoichiometric rhodium phorphyrin complexes.[48,49] In this transformation, PCP is catalytically converted to 4,4′-dimethyl-bibenzyl **113** under two possible conditions (eqn (29)). Rh^{III}(ttp)I (ttp = tetratolylporphyrinato dianion) in the presence of KOH (1 equiv.) provided the cleaved product **113** in 83% yield in 25 h; with Rh^{III}(ttp)Me, the product was obtained in 78% after 54 h. Independent deuterium labeling experiments showed that water is the source of hydrogen and that the C–C activation does not involve C–H activation intermediates. The proposed catalytic cycle, which is supported by experimental data, is shown in Scheme 18. Hydrolysis of either precatalyst **114** or **115** provides Rh^{III}(ttp)OH (**116**), which can decompose to Rh^{II}(ttp) radical and exist in an equilibrium with $Rh^{II}(ttp)_2$. Two equivalents of Rh^{II}(ttp) react with PCP to form complex **117**; kinetic data supports an overall third-order reaction, first order in PCP and second order in Rh^{II}(ttp). Finally, reaction with H_2O provides **113** and regenerates the initial catalyst **116**.



(29)

Conclusion

In summary, a variety of stoichiometric and catalytic C–C activation reactions have been presented with a discussion of the differing mechanistic pathways that are involved. Although many examples may appear to be special cases, they demonstrate the potential to develop generalized methodologies and strategies. With improvements in this field, it should become possible to construct compounds non-traditionally using novel bond disconnections. In fact, as the field has moved forward from stoichiometric reactions to the development of new catalytic C–C activation transformations, the synthetic utility of this approach has become more apparent. Future improvements in this field would involve moving away from specific examples and developing more general methods for catalytic C–C activation of more common substrates. This will likely require the evolution of new types of catalysts or strategies. We expect, in the coming years, C–C activation will emerge to have a profound impact, in both academia and industry, on accessing synthetically useful molecules.

Acknowledgments

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Abbreviations

Acac	Acetylacetone
C–C	Carbon–carbon
C–H	Carbon–hydrogen
C_2H_4	Ethylene
COD	Cyclooctadiene
COE	Cyclooctene
DMI	N,N′-Dimethylimidazolidinone
dppBz	1,2-Bis(diphenylphosphino)benzene
dppf	1,1′-Bis(diphenylphosphino)ferrocene

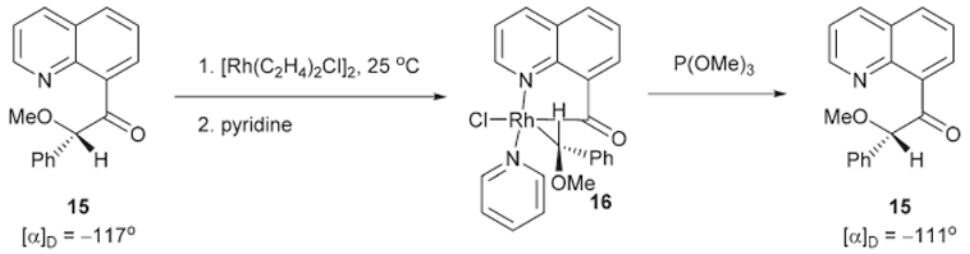
NMR	Nuclear magnetic resonance
PCy_3	Tricyclohexylphosphine
PCP	[2.2]paracyclophane
$P(OMe)_3$	Trimethylphosphite
PPh_3	Triphenylphosphine
THF	Tetrahydrofuran
ttp	Tetratolylporphyrinato dianion

Biographies

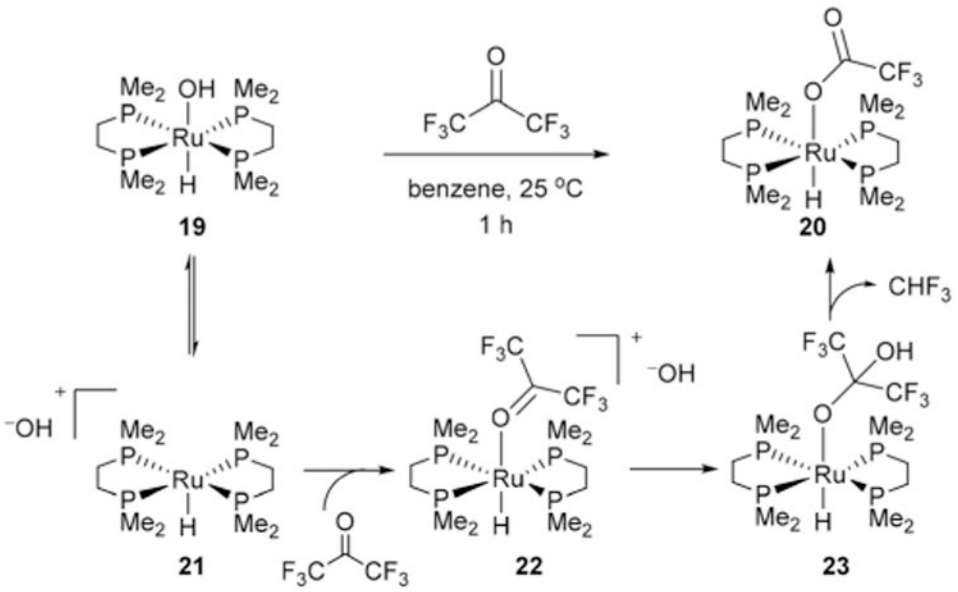
Alpay Dermenci was born in Huntington Beach, CA (USA) in 1984. He received his B.S. from University of California, Irvine and carried out his doctoral studies under the guidance of Prof. Scott J. Miller at Yale University. His research focused on the application and development of amino acids and peptides as catalysts for the synthesis of natural products. Following his Ph.D., he conducted post-doctoral studies with Prof. Guangbin Dong at UT Austin focusing on the development of C–C activation methodology. Alpay is currently a research scientist at Pfizer, Inc. in Groton, CT.

Jotham W. Coe, a Research Fellow at Pfizer, is a medicinal chemist in BioTherapeutics working towards treatments for inflammatory conditions. Coe spent 15 years in the Neuroscience Department (CNS) pursuing medicines for depression, schizophrenia, ADHD and addiction, where he was directly involved in the discovery of Chantix (Champix), an aid to smoking cessation. Coe earned his A.B. degree in chemistry from Harvard College in 1981, worked 2 years at SISA Pharmaceutical Laboratories, then entered MIT to study with Professor William R. Roush. He received his Ph.D. degree in 1988 and joined Pfizer Central Research. Coe has published extensively in the area of organic and medicinal chemistry with a focus on reaction mechanism and synthesis and has received numerous patents in the areas of oncology, neuroscience and inflammation.

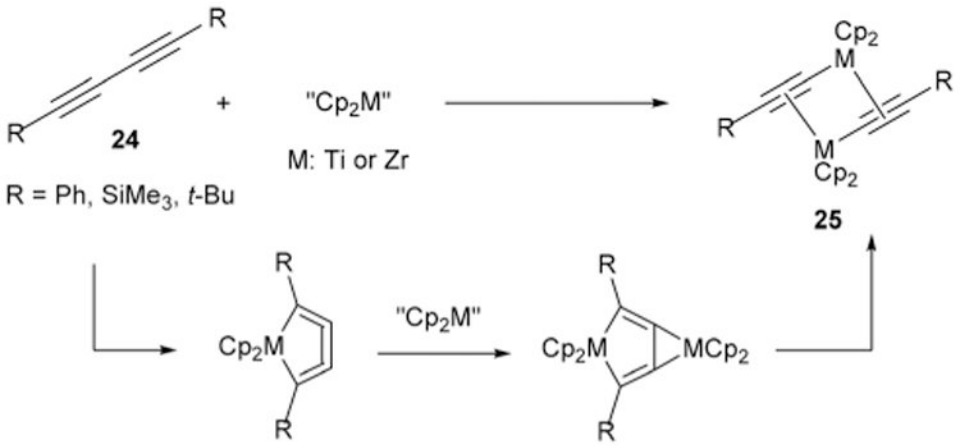
Guangbin Dong received his B.S. degree from Peking University and completed his Ph.D. degree in chemistry from Stanford University with Professor Barry M. Trost, where he was a Larry Yung Stanford Graduate fellow. In 2009, He began to research with Prof. Robert H. Grubbs at California Institute of Technology, as a Camille and Henry Dreyfus Environmental Chemistry Fellow. In 2011, he joined the department of chemistry and biochemistry at the University of Texas at Austin as an assistant professor and a CPRIT Scholar. His research interests lie at the development of powerful chemical tools for addressing questions of biological importance.



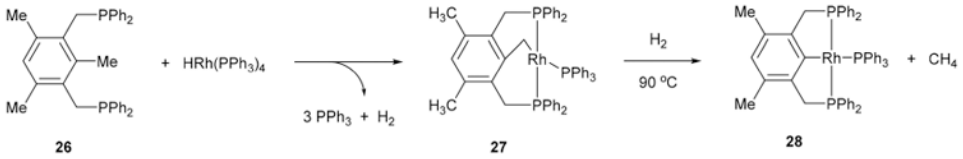
Scheme 1.
Rh-promoted C–C activation of a chiral quinoline derived substrate.



Scheme 2.
Ru-promoted C–C activation of hexafluoroketone.

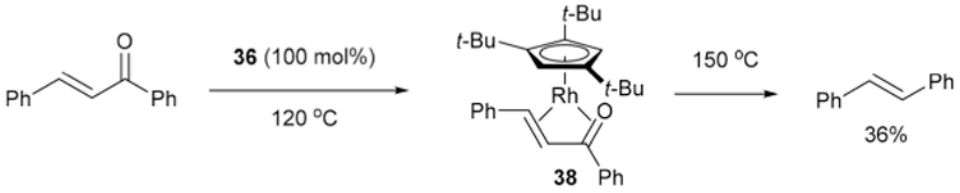


Scheme 3.
Zr- and Ti-mediated C–C activation of diynes.

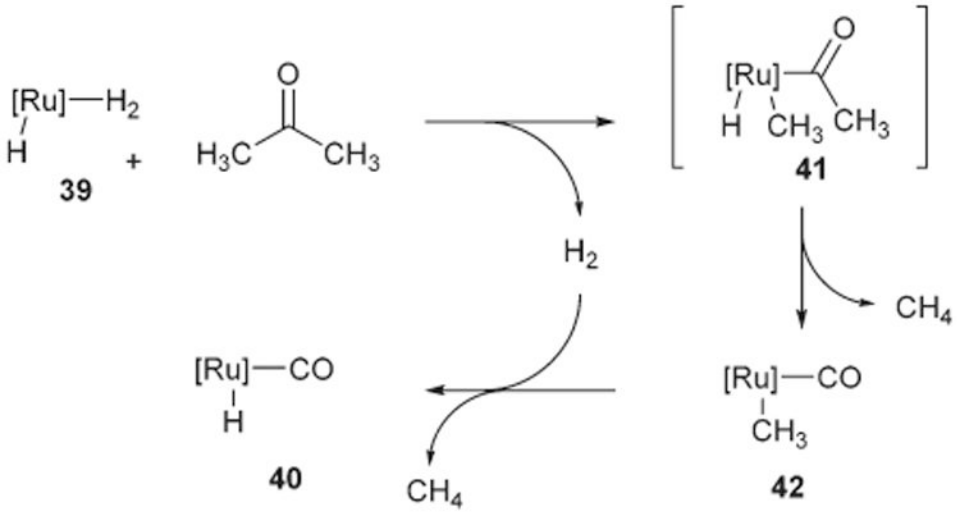


Scheme 4.

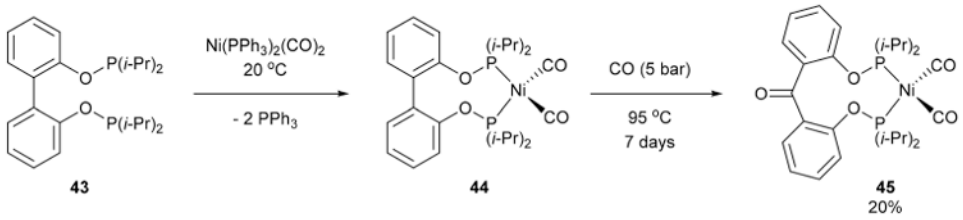
Activation of strong C–C bonds in pincer ligands reported by Milstein and co-workers.



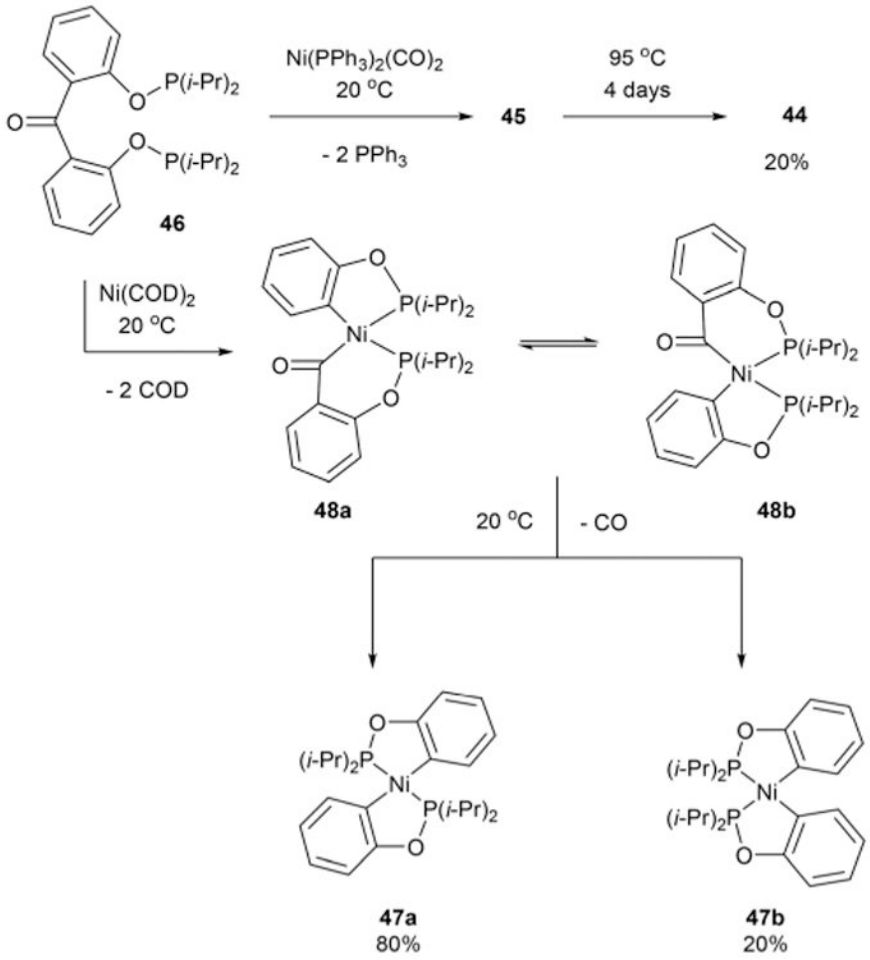
Scheme 5.
Decarbonylation of chalcone by unique Rh complex **36**.



Scheme 6.
Demethylation of acetone *via* C-C activation.

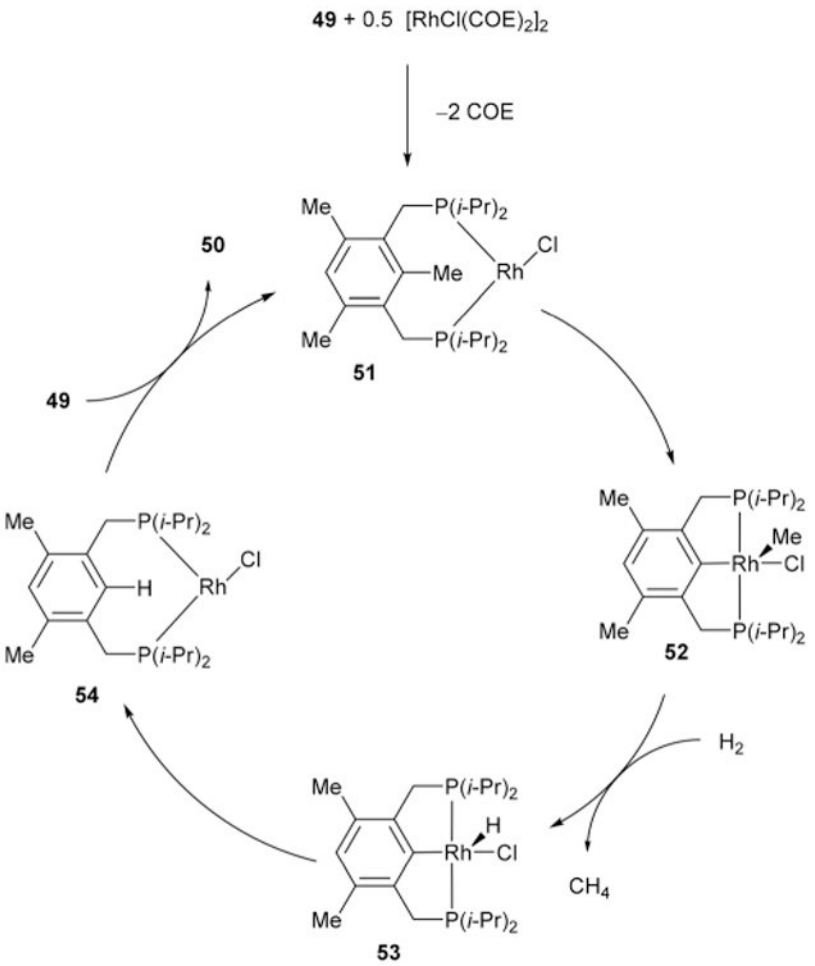


Scheme 7.
Phosphonite-directed C–C activation and carbonylation with Ni.

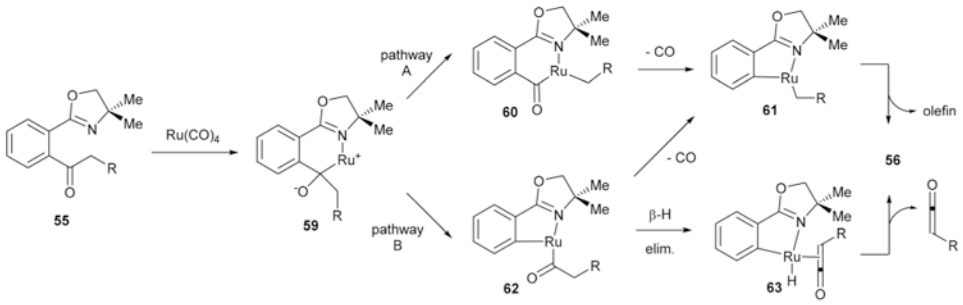


Scheme 8.

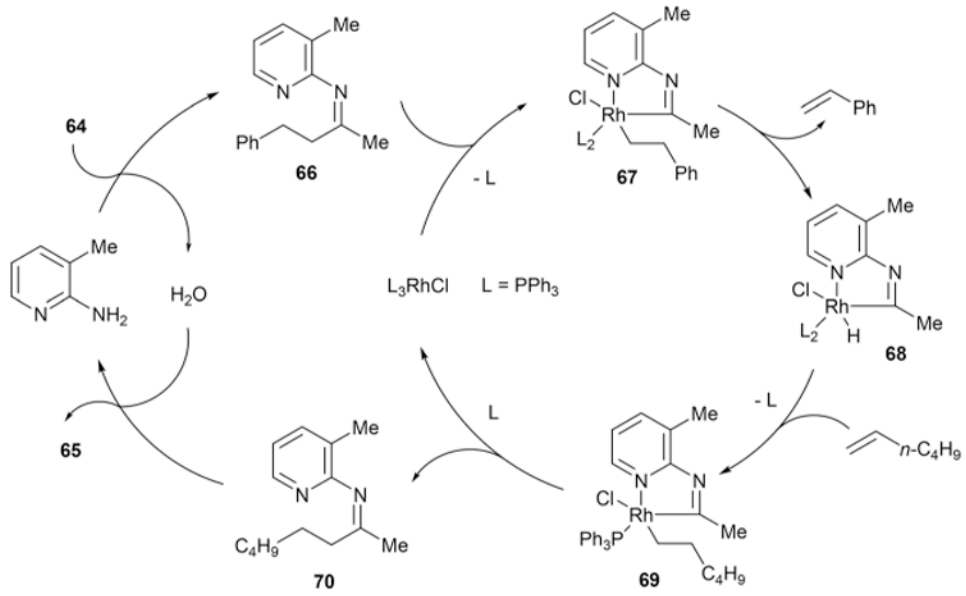
C–C activation and decarbonylation of benzophenone with Ni as the metal center.



Scheme 9.
Proposed catalytic cycle for C–C activation of PCP ligand.

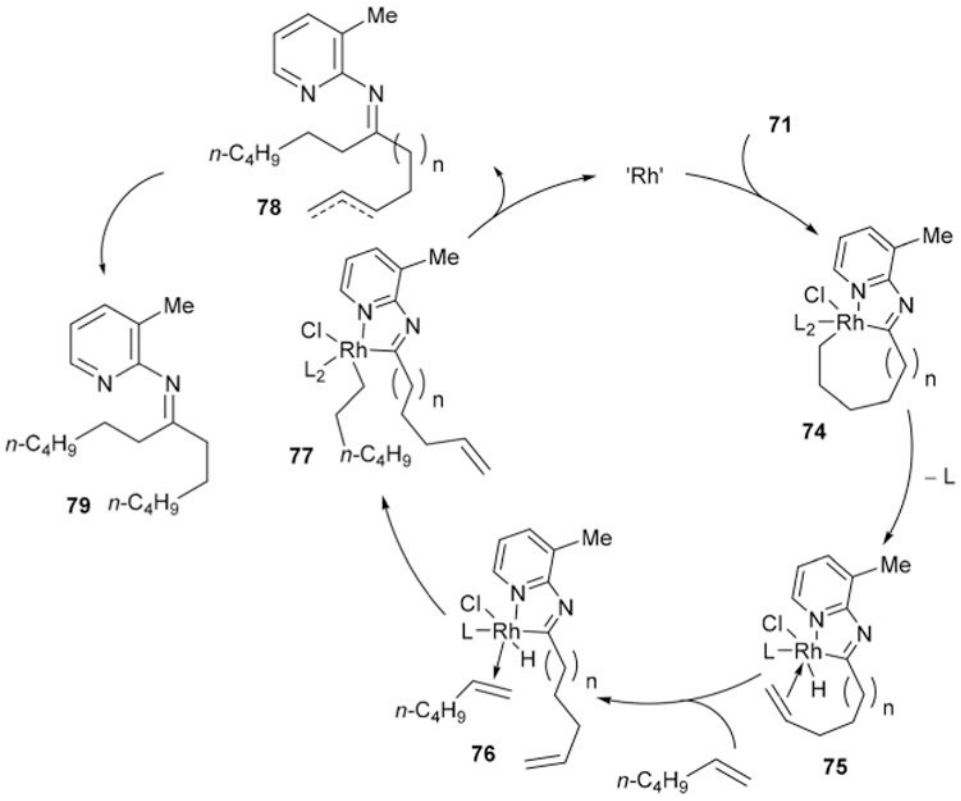


Scheme 10.
Proposed mechanism for oxazoline-directed C–C activation.

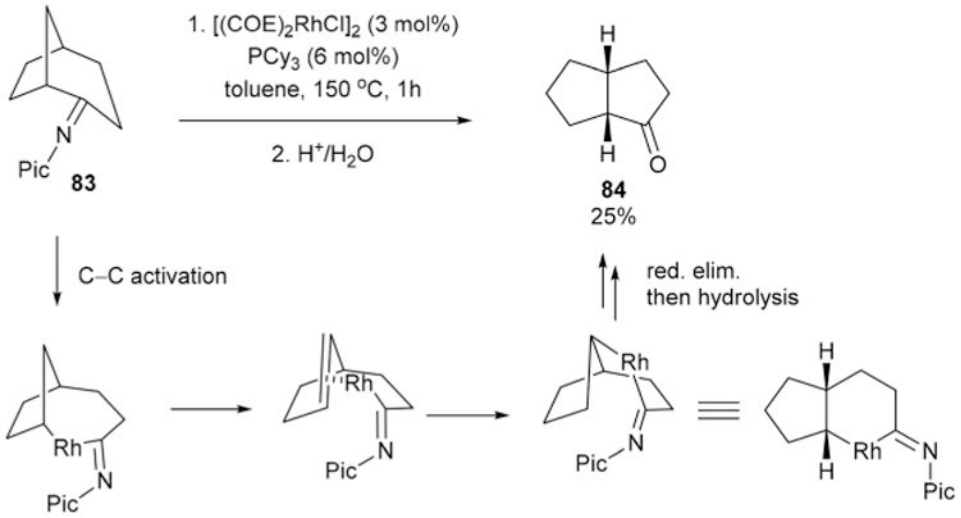


Scheme 11.

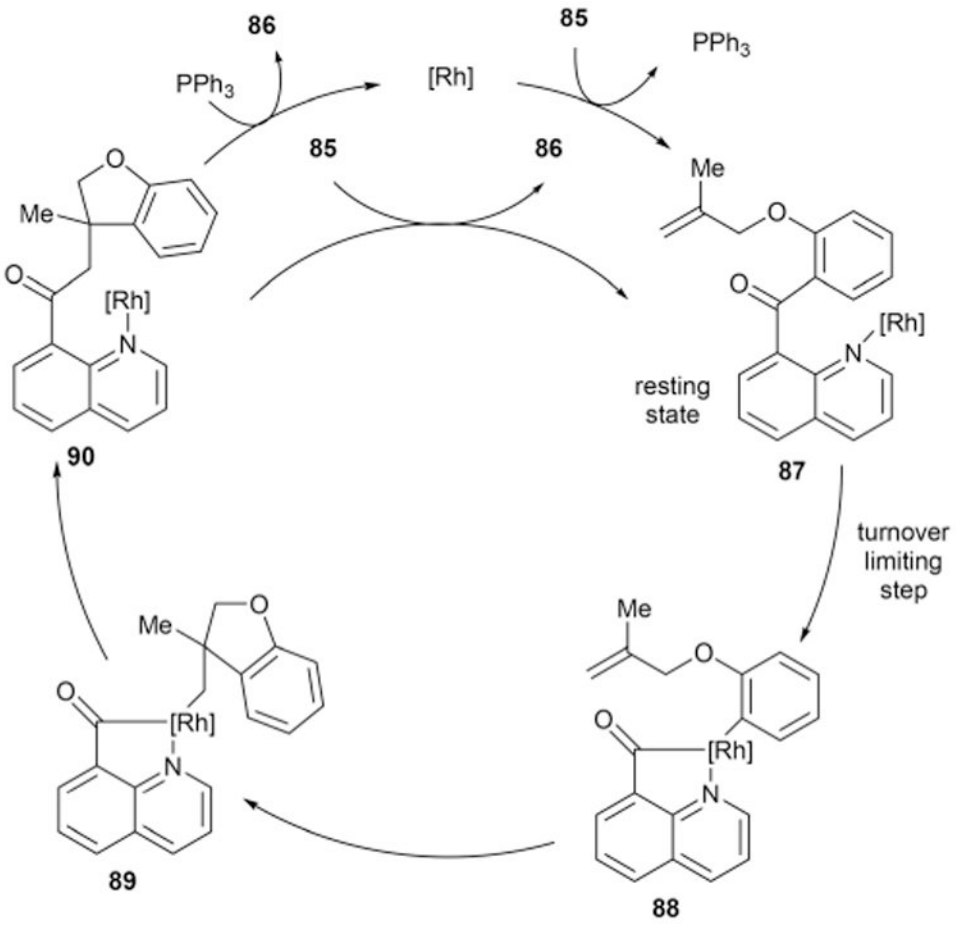
Mechanism of alkyl-exchange *via* C–C bond activation.



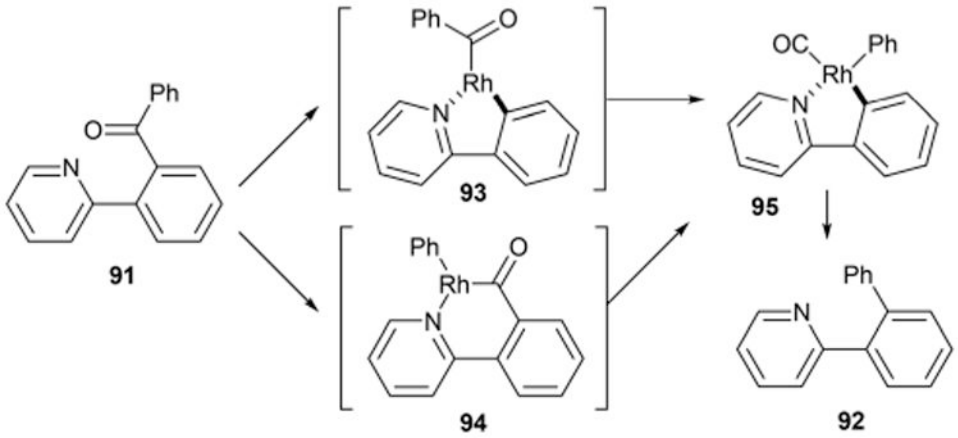
Scheme 12.
Proposed mechanism for Rh-catalyzed ring-opening of cycloalkanoketimines.



Scheme 13.
Rh-catalyzed skeletal rearrangement of bicycle[3.2.1]octan-2-one.

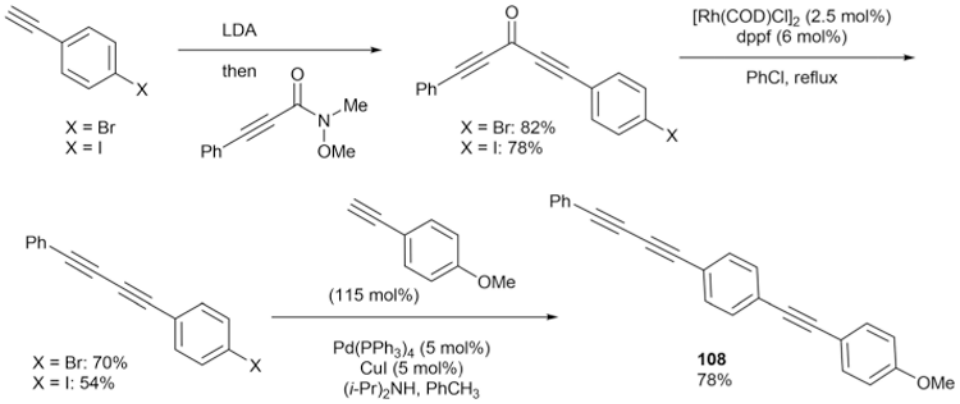


Scheme 14.
Mechanism for the synthesis of all carbon quaternary centers.



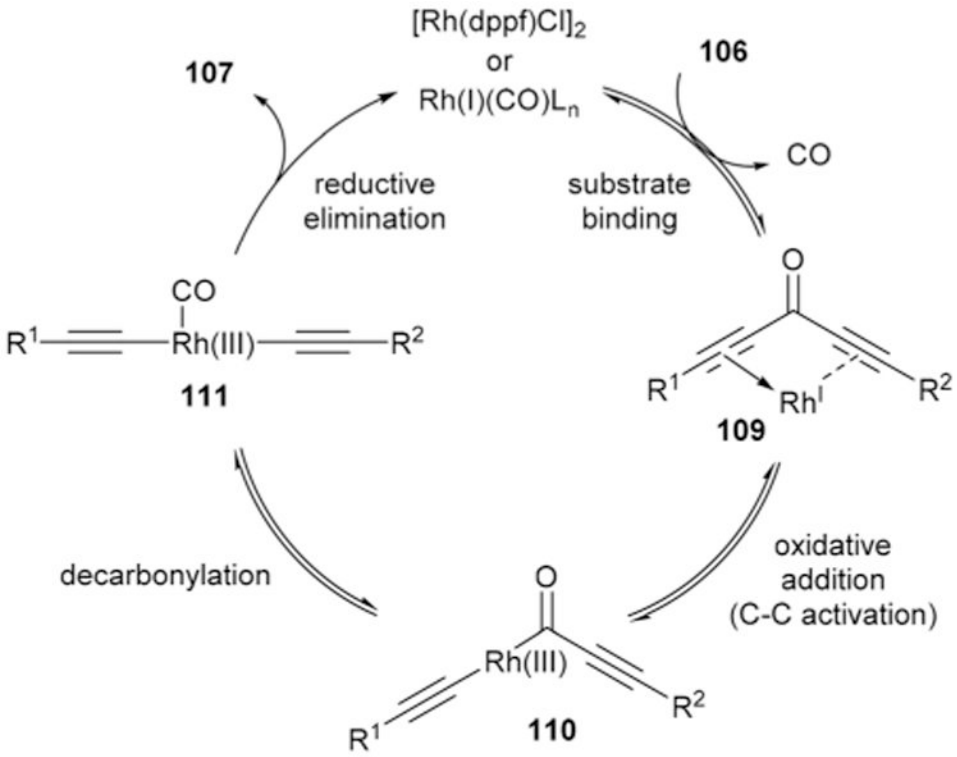
Scheme 15.

Proposed catalytic cycle for the C–C activation and decar-bonylation of biaryl ketones.

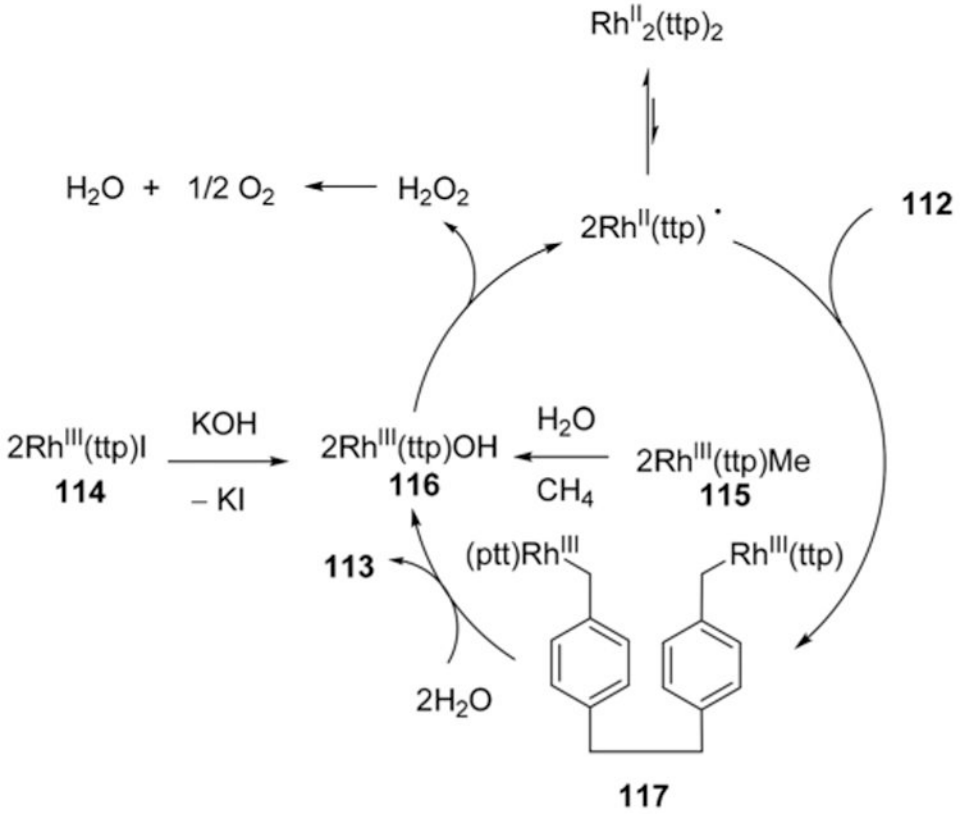


Scheme 16.

Utilization of the Rh-catalyzed decarbonylation to synthesize highly conjugated rod-like structures.



Scheme 17.
Proposed mechanism for the Rh-catalyzed decarbonylation of diynones.



Scheme 18.
The proposed mechanism for Rh-catalyzed cleavage of PCP.