CATALYTIC CLEAVAGE OF CARBON-CARBON SIGMA BONDS BY TRANSITION METALS

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INTRODUCTION

The selective cleavage of carbon-carbon (C-C) sigma bonds is one of the most difficult challenges in organometallic chemistry. The lack of reactivity of these bonds can be attributed to their thermodynamic stability and kinetic inertness. Unlike the activation of C-H bonds, which produces a strong metal-hydrogen bond (60 - 70 kcal mol^{-1}), the oxidative addition of a C-C bond onto a transition metal center forms two relatively weak metal-carbon bonds (20 - 40 kcal mol^{-1} per bond) at the expense of a strong C-C bond (*ca.* 85 kcal mol^{-1}).[1] Furthermore, the constrained directionality and steric inaccessibility of the C-C σ-orbital contribute to a high activation barrier for C-C bond activation.[2] In addition to overcoming thermodynamic and kinetic challenges, selective C-C bond cleavage must occur in the presence of more reactive bonds such as C-X (X = N, O, Br, Cl, etc.) and C-H bonds.

Despite these challenges, various chemical transformations of C-C sigma bonds by homogenous transition metal catalysts have been achieved in the past two decades. Two basic strategies that have been employed to facilitate C-C bond cleavage are 1) the use of reactive starting materials and 2) the generation of highly stabilized products. The first strategy is exemplified by the reaction of strained substrates, such as cyclopropanes and cyclobutanes. The second strategy includes the aromatization of prearomatic compounds and the formation of cyclometallated products through chelation-assistance. Another method often employed in C-C bond activation is the selection of substrates with metal-coordinating functional groups such as carbonyls, alcohols, and nitriles. In order to understand both the chemical reactivity and future potential of C-C sigma bond activation, the different strategies of metal-mediated C-C bond cleavage from the initial stoichiometric reactions to current catalytic processes will be discussed.

UTILIZATION OF STRAINED MOLECULES

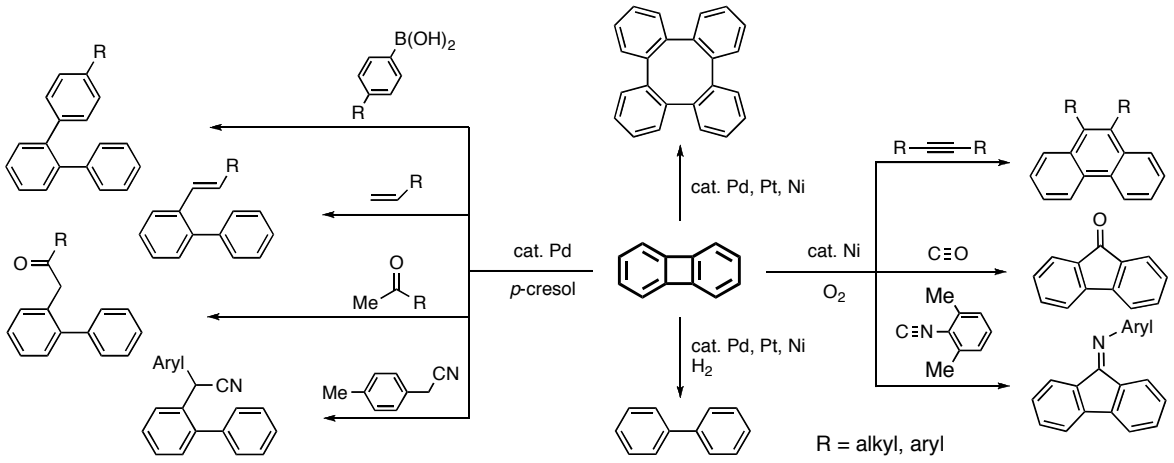
The utilization of ring strain is the most employed strategy for transition metal-catalyzed C-C bond cleavage. Unlike typical C-C bonds, the C-C sigma bonding orbital of highly strained 3- and 4-membered carbocyclic rings is not constrained along the internuclear axis. The outward bend of these bonds allows for greater accessibility, lowering the kinetic barrier for C-C bond activation. Furthermore, the relief of strain gained from forming stable 4- and 5-membered metallacyclic intermediates provides a

strong thermodynamic driving force for these reactions. The first example of a metal-mediated cleavage of a C-C sigma bond dates back to Tipper's 1955 report of the reaction between $PtCl_2$ and cyclopropane.[3] Since then, numerous reports have been published describing the mechanism of C-C bond cleavage in strained ring systems, and many advances have been made in the discovery of novel and synthetically useful C-C bond cleavage reactions.

Examples of Catalytic Ring Expansion Reactions

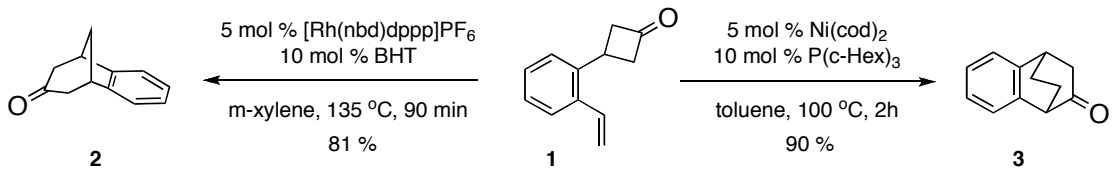
The direct insertion of late transition metals (Fe, Ni, Ir, Pt, Pd, etc) into the strained C-C sigma bond of biphenylene has been extensively documented.[4] These compounds undergo a variety of insertion reactions with small molecules, leading to the formation of various functionalized aromatic compounds (Scheme 1). Jones reported the nickel-catalyzed coupling of biphenylene with alkynes, carbon monoxide, and isocyanides to form phenanthrenes, fluorenone, and fluorenimines, respectively.[5] Biphenylene has also been employed in various palladium-catalyzed cross-coupling reactions to generate substituted biphenyls.[6]

Scheme 1. Reactions with biphenylene.



In addition, the insertion of unsaturated C-C bonds into a sigma bond is a potentially useful method for forming expanded carbon frameworks. A representative example is the rhodium-catalyzed intramolecular olefin insertion of 3-(*o*-styryl)cyclobutanone **1** to generate benzobicyclo[3.2.1]octenone **2** (Scheme 2).[7] Interestingly, the reaction of **1** with a nickel catalyst afforded benzobicyclo[2.2.2]octenone **3**.[8] The different products observed are explained by divergent C-C bond cleavage mechanisms. In the rhodium–catalyzed reaction, C-C bond cleavage is proposed to occur through a metal insertion into the α-keto C-C bond, whereas the nickel-catalyzed process occurs through an intramolecular oxidative cyclization of the olefin and carbonyl group to form an oxanickelacyclopentane intermediate followed by β-carbon elimination.

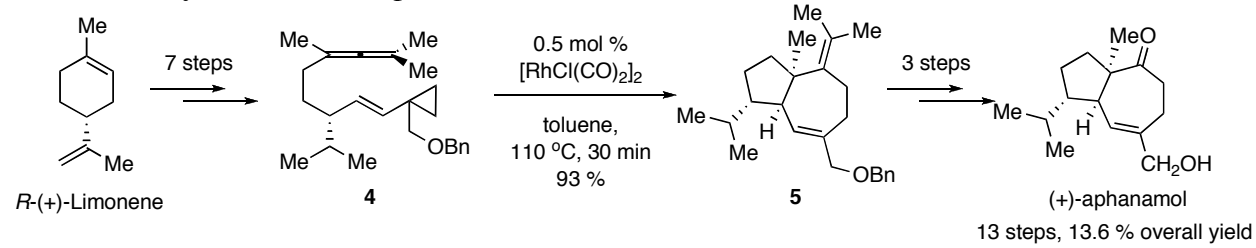
Scheme 2. Metal-catalyzed intramolecular olefin insertion of 3-(*o*-styryl)cyclobutanone.



Applications in Total Synthesis

Wender has demonstrated the synthetic potential of strain-assisted C-C bond cleavage through the use of vinylcyclopropanes and vinylcyclobutanones to produce various seven-, eight- and nine-membered rings. Examples include the [5+2] cycloaddition of vinylcyclopropanes and π-systems, the [5+2+1] and [5+1+2+1] cycloadditions of vinylcyclopropanes, π-systems and CO, and the [6+2] cycloaddition of vinylcyclobutanones and π-systems.[9] An example of the practical application of metal-catalyzed C-C bond cleavage is the total synthesis of (+)-aphanamol I.[10] A key step in the synthesis is the intramolecular allenyl [5+2] cycloaddition of **4** to generate the cycloadduct **5** (Scheme 3).

Scheme 3. Total synthesis of (+)-aphanamol I.



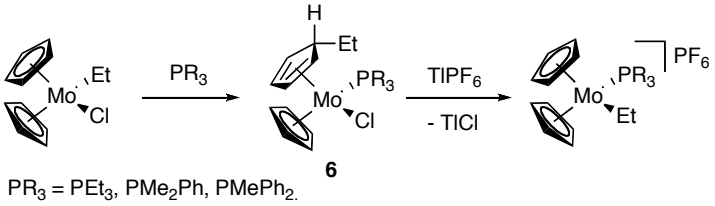
UTILIZATION OF AROMATIZATION

For unstrained molecules, aromatization provides a strong driving force for C-C bond cleavage and renders the reaction thermodynamically feasible. Although the first example of metal-mediated C-C bond cleavage *via* aromatization was reported in 1969 by Maitlis using Dewar benzene,[11] this strategy is arguably the least developed C-C bond cleavage method. Few stoichiometric C-C bond cleavage reactions driven by aromatization have been published, and no catalytic processes involving unstrained molecules have been reported to date.

Examples of Stoichiometric C-C Bond Cleavage *via* Aromatization

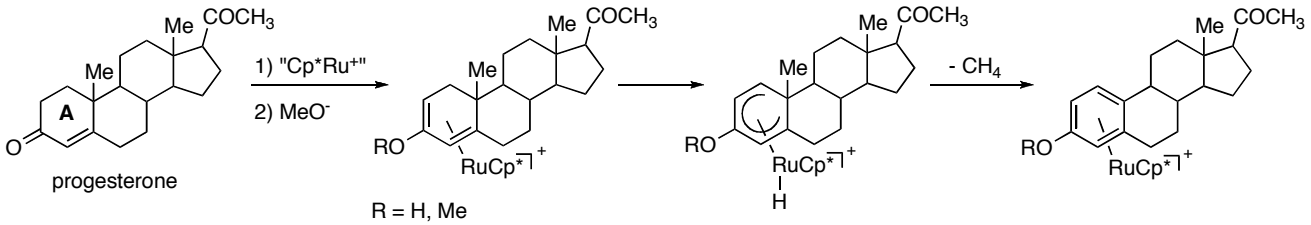
An example of reversible C-C bond cleavage was reported by Green using a bis(cyclopentadienyl) molybdenum complex (Scheme 4).[12] The ligated ethyl group migrated from the metal center to an adjacent Cp ligand (Cp = cyclopentadienyl) upon the addition of phosphine to afford an η^4-cyclopentadiene complex **6**. Abstraction of the chloride anion opened a vacant coordination site on the metal, resulting in the return of the *endo*-ethyl group onto the metal center.

Scheme 4. C-C bond cleavage via aromatization strategy.



Chaudret applied the aromatic stabilization strategy to eliminate the methyl group in a series of steroid compounds.[13] The reaction of the electrophilic fragment $[Cp^*Ru]^+$ with the A ring of steroids resulted in the aromatization of the ring and formation of a stable η^6-arene complex. A representative example using progesterone is shown in Scheme 5. The driving force for these reactions is the remarkably high affinity of the cationic ruthenium fragment for aromatic hydrocarbons. In addition, the mechanism is proposed to proceed through a radical process based upon the observation of ethane formation.

Scheme 5. Aromatization of the A ring of progesterone by $[Cp^*Ru]^+$.



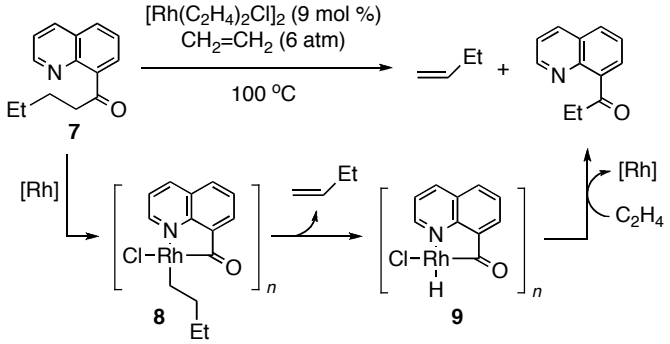
UTILIZATION OF CHELATING SUBSTRATES

For the C-C bond cleavage of unstrained molecules, directed cleavage by chelation-assistance is one of the most promising methods. This strategy requires a coordinating functional group on the substrate that can direct the metal to the bond to be cleaved, resulting in the formation of a stable five-membered metallocycle.

Chelation Assistance using Model Compounds

One of the representative examples of this strategy is the catalytic activation of an α-keto C-C bond in the model compound 8-quinolinyl butyl ketone **7**, developed by Suggs (Scheme 6).[14,15] The C-C bond cleavage by Rh(I) occurs through a concerted oxidative addition without prior C-H activation.[16] By coordination to the nitrogen atom of **7**, the metal is directed to the α-keto C-C bond, resulting in selective activation. In the presence of excess ethylene, **7** was quantitatively converted from

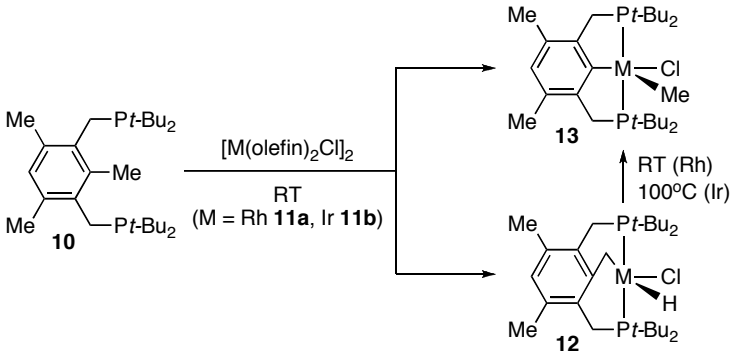
Scheme 6. Rh(I)-catalyzed alkyl transfer with 8-quinolinyl alkyl ketone.



a butyl ketone to an ethyl ketone. The mechanism involves an α-C-C bond cleavage to form the acylrhodium(III) butyl intermediate **8** followed by β-hydrogen elimination and subsequent insertion of ethylene into the acylrhodium(III) hydride **9**. Similar model complexes with oxazoline and pyridine directing groups have been developed by Murai for the Ru-catalyzed, decarbonylative C-C bond cleavage of alkyl phenyl ketones.[17]

Milstein demonstrated with a bulky pincer-type ligand **10** that metal insertion into an unstrained, strong C_{Me}-C_{aryl} bond can be both thermodynamically and kinetically preferred over the competing insertion into a benzylic C-H bond.[18] The stoichiometric reaction of rhodium and iridium olefin dimers (**11a** and **11b**) with **10** resulted in the concurrent formation of C-H and C-C activation products at room temperature (Scheme 7). The product of C-H activation, complex **12**, is quantitatively converted into the C-C activation product, complex **13**, at room temperature (**11a**) or upon moderate heating (**11b**). The kinetic barrier for C-C oxidative addition was determined to be slightly lower than that for C-H ($\Delta\Delta G^{\ddagger}_{CH\text{-}CC}$ = 0.3 (M = Ir), 0.5 kcal mol^{-1} (M = Rh)). In addition, this reaction has been modified into a catalytic process by using an energy-releasing step such as hydrogenolysis to give demethylated phosphine ligand and methane.[19]

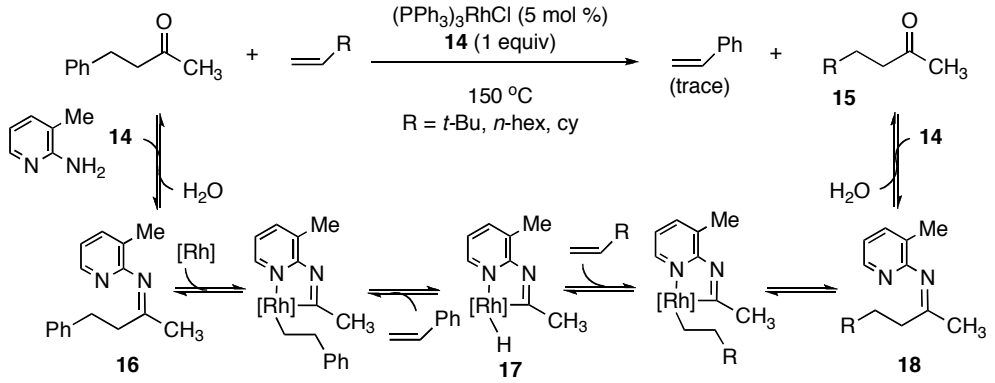
Scheme 7. Reaction of *t*-Bu-PCP with $[M(olefin)_2Cl]_2$ M = Rh, Ir.



Reversible Chelation Assistance using 2-Amino-3-Picoline

The chelation-assistance strategy has been extended by Jun through the use of a temporary chelating auxiliary such as 2-amino-3-picoline **14**, which can be easily removed from the product by hydrolysis.[20] The reaction of an unstrained ketone such as benzylacetone with excess olefin, **14**, and catalytic Wilkinson's complex gave **15** and a trace amount of styrene.[21] Since the reaction is in thermodynamic equilibrium, the removal of styrene through polymerization at the reaction temperature and the addition of excess olefin were crucial to drive the reaction forward. As illustrated in Scheme 8, initially ketimine **16** is formed from benzylacetone and **14**. Subsequent C-C bond activation followed by β-hydrogen elimination gives (iminoacyl)rhodium(III) hydride **17** and styrene. The hydrometalation of an olefin by **17** followed by reductive elimination produces ketimine **18**, which hydrolyzes to **15**. The same catalytic system was employed in the C-C bond activation of secondary alcohols to form the corresponding alkyl group-exchanged ketone.[22]

Scheme 8. Rh(I)-catalyzed alkyl group transfer using 2-amino-3-picoline.



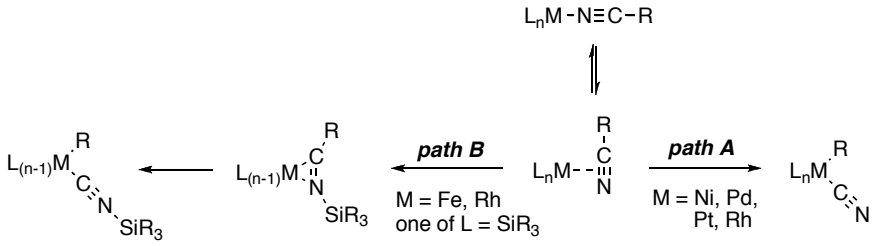
UTILIZATION OF ACTIVATING FUNCTIONAL GROUPS

The α-C-C bonds to carbonyls, alcohols, and nitriles are often the targets for activation due to the inherent metal-coordinating ability of these functional groups.[23] Rh(I) insertion into the α-keto C-C bond of strained cyclobutanones[24] and cyclopropenones,[25] as well as unstrained α- and β-diketones[26] and cycloalkanones[27] is well documented in the literature. Additionally, β-carbon elimination from transition metal alkoxides, formed from the reaction of a metal complex with a tertiary alcohol, has been reported for various transition metals.[28,29] In order to illustrate the potential of this general class of C-C bond cleavage reactions, this section will focus on the development of transition metal-catalyzed C-CN bond cleavage.

Mechanism of C-CN Bond Cleavage

The cyano group is considered an "active" functional group due to its ability to coordinate to transition metals in an η^1-fashion or η^2-fashion.[30] In particular, η^2-coordination is known to trigger the activation of a C-CN bond via oxidative addition (path A) or via formation of silylisonitrile complexes when a Lewis acidic silyl group is ligated on the metal (path B) (Scheme 9). Transition metal complexes that have been reported to cleave the C-CN bond through an oxidative addition mechanism mainly involve Group 10 transition metals (Ni, Pd, Pt), whereas cleavage through deinsertion of silyl isocyanide is often demonstrated by Rh, Ir, and Fe complexes. Cleavage of the C-CN bond was reported as early as 1971.[31] Since then, several reports of catalytic C-CN bond cleavage reactions have been published.

Scheme 9. Activation of C-CN bonds by transition metal complexes.

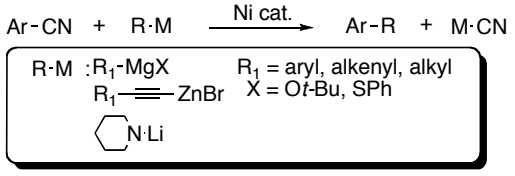


Examples of Catalytic C-CN Bond Cleavage

A significant example of C-CN bond cleavage is the extension of typical cross-coupling partners (i.e. aryl halides and aryl sulfonates) to include aryl cyanides. Using a nickel catalyst, an efficient cross-coupling reaction employing aryl cyanides and various organometallic reagents was achieved (eq. 1). Substituted aryl cyanides underwent sp^2-sp^2 and sp^2-sp^3 cross-coupling with alkoxy-modified Grignard reagents,[32,33] while alkynylzinc reagents and lithium amides were discovered to be suitable nucleophiles for alkynylation and amination.[34,35] Another example involving the catalytic cleavage of C-CN bonds is the Ni(0)-catalyzed carbocyanation of internal alkynes, recently developed by Nakao and Hiyama (eq. 2).[36,37] Insertion of the alkyne into the C-CN bond is proposed to occur through oxidative addition of the C-CN bond to the Ni(0) (Scheme 9, path A), alkyne insertion into the Ni-CN bond, and subsequent reductive elimination to give the carbocyanation product.[23]

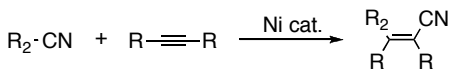
In addition to the previous examples, Nakazawa reported the photocatalytic decyanation of acetonitrile and aryl cyanides using $Cp(CO)_2FeMe$ and Et_3SiH (eq. 3).[38] Unlike the nickel-catalyzed reactions, a silyliron complex was identified as the active catalytic species and the mechanism is proposed to proceed through a deinsertion of silyl isocyanide (Scheme 9, path B).[39]

Miller:



(1)

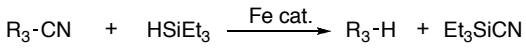
Hiyama:



R_2 = aryl. allyl, alkenyl, Me

(2)

Nakazawa:



R_3 = aryl, Me

(3)

CONCLUSION

The selective cleavage of C-C sigma bonds by transition metal complexes has received growing scientific interest in the past two decades, due not only to its fundamental challenge but also its potential utility in organic synthesis. First and foremost, these advances illustrate that C-C bond cleavage is not a "forbidden" process. Several strategies have been employed to overcome the thermodynamic and kinetic barriers of C-C bond activation, such as the relief of ring strain, the drive of product aromatization, the formation of stable metallacyclic intermediates, and the use of substrates bearing chelating functional groups. Despite these advances, the development of synthetically useful, catalytic C-C bond transformations is still in its infancy and is currently limited by substrate scope and lack of product complexity. Further mechanistic understanding and methodological exploration will likely advance the

synthetic usefulness of this class of reactions and bring increased attention to this challenging area of organometallic chemistry.

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