Top Curr Chem (2014) 346: 233–258
DOI: 10.1007/128_2014_545

Published online: 23 April 2014

Transition Metal-Catalyzed C–C Bond Activation of Four-Membered Cyclic Ketones

Tao Xu, Alpay Dermenci, and Guangbin Dong

Abstract With the advent of new synthetic methodologies, carbon–carbon bond (C–C) activation strategies have uncovered not only new fundamental reactivity but also the potential for use as a highly efficient synthetic protocol. This chapter specifically discusses the use of four-membered ketone-based starting materials for C–C activation initiated transformations using a variety of transition metals. The two major modes of activation, oxidative addition and β-C elimination, are presented as each pathway shows different mechanistic details and the ability to effect several types of reactions. Applications to the synthesis of complex molecules are presented and perspectives on future applications are considered.

Keywords β-Carbon elimination · C–C activation · Cycloaddition · Oxidative addition

Contents

T. Xu and G. Dong (✉)
Department of Chemistry and Biochemistry, University of Texas at Austin, 1 University Station A5300, Austin, TX 78712-0165, USA
e-mail: gbdong@cm.utexas.edu

A. Dermenci
Department of Chemistry and Biochemistry, University of Texas at Austin, 1 University Station A5300, Austin, TX 78712-0165, USA

Pfizer Inc., Worldwide Medicinal Chemistry, 445 Eastern Point Road, Groton, CT 06340, USA

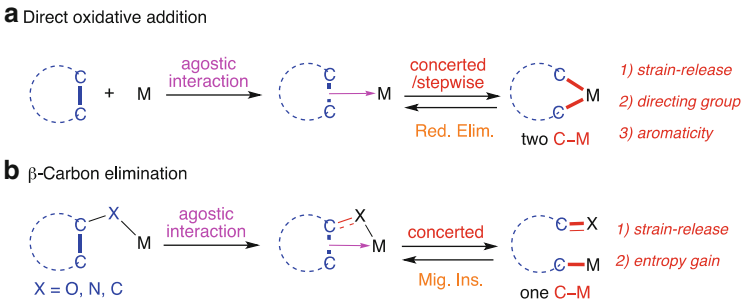
1 Introduction

Given the ubiquity of carbon–carbon (C–C) and carbon–hydrogen (C–H) bonds, the ability to disconnect and/or functionalize either selectively would provide synthetic chemists with an atom-economic [1] and straightforward method to construct biologically interesting or complex molecules [2–5]. In contrast to the developing and fruitful area of C–H functionalization ([6] and references cited therein), C–C activation/functionalization is less developed, emerging as a new area in the synthetic community [7–9]. In general, there are two primary modes of C–C single bond cleavage: direct oxidative addition (Scheme 1A), and β-carbon elimination (Scheme 1B).

The challenges associated with oxidative addition of a C–C bond onto a transition metal are twofold. First, the reductive elimination (reverse reaction of oxidative addition) is usually an exergonic reaction and thus thermodynamically favored, which makes the oxidative addition of C–C bonds disfavored and therefore a sluggish process. More often than not, oxidative additions take place at high temperature or need other driving forces such as strain release, forming aromatic compounds, and/or chelation-derived assistance [10, 11]. Second, C–C bonds typically have neighboring C–H bonds that are more "exposed" which causes kinetic competition to C–C bond activation [12–14]. In other words, during interaction with a transition metal, C–H activation is often more favorable due to the statistical abundance and favorable orbital trajectory of C–H bonds.

Regarding the second mode of C–C activation, β-carbon elimination poses similar challenges, though as a primarily intramolecular process it does not involve the same kinetic barriers with a transition metal. Furthermore, when acyclic substrates are employed, a byproduct is generated alongside the β-C elimination reaction. In this case, the β-C elimination process generates an entropy increase, lowering the activation barrier. However, generally, transition metal-mediated β-C elimination reactions are still thermodynamically challenging due to formation of weak metal–carbon bonds, and often less competitive compared to the more common β-H elimination.

Due to the above-mentioned thermodynamic and kinetic challenges to cleave C–C σ bonds, strain-release provided by small-sized rings serves as one of the most important driving forces for C–C activation. A large number of novel and synthetically useful transformations based on this mode of reactivity have been realized, particularly during the past two decades. For example, reactions with



Scheme 1 Two methods to activate C–C bonds

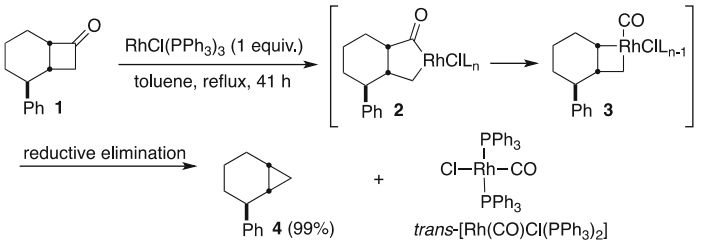
cyclopropanes are of high synthetic value, and have been extensively developed [15] and reviewed. However, activation of the related four-membered ring compounds has received much less attention [16]. In particular, the four-membered ring compounds containing a ketone moiety are unique substrates, because the carbonyl can serve as a reacting group or a convenient handle to control site-selectivity (see below). On the other hand, given the possibility for decarbonylation (see below), these compounds can behave as either a four-carbon or a three-carbon synthon, leading to distinct transformations. Herein, while a number of excellent reviews on C–C activation have been reported previously [9–16], this review specially focuses on C–C bond cleavage and further transformations of four-membered ring ketones, including cyclobutanones, cyclobutenone/benzocyclobutenones, and cyclobutenediones/benzocyclobutenediones.

2 C–C Bond Activation of Cyclobutanones

Seminal studies of C–C bond activation [17–25] demonstrated that C–C bonds adjacent to a carbonyl group are subject to C–C bond cleavage when treated with late transition metals. The pioneering work by Murakami and Ito showed that cyclobutanones are suitable substrates for catalytic C–C bond activation transformations.

2.1 Rh-Catalyzed C–C Bond Activation via Oxidative Addition

In 1994, Murakami and co-workers [26] found that when cyclobutanone (**1**) was treated with an equimolar amount of $(PPh_3)_3RhCl$ in refluxing toluene, decarbonylation took place to produce cyclopropane (**4**) in quantitative yield along with the unreactive complex *trans*-$[Rh(CO)Cl(PPh_3)_2]$ (1):



(1)

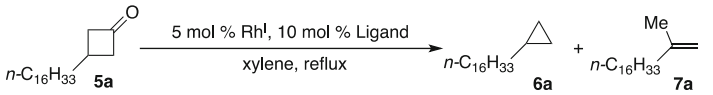
This decarbonylation reaction was initially believed to proceed through direct oxidative addition of Rh onto the less hindered C–C bond adjacent to the carbonyl group to give five-membered rhodacycle (**2**), followed by carbon monoxide extrusion to yield the four-membered rhodacycle (**3**), which then undergoes reductive elimination to furnish the observed product (**4**). These results are in firm agreement with a stoichiometric decarbonylation reaction previously reported by Rusina [27]. Formation of the thermodynamically stable but catalytically inert *trans*-[Rh(CO)Cl$(PPh_3)_2$] and release of the ring strain are two major driving forces for this reaction.

A more detailed study [28] found that *trans*-[Rh(CO)Cl$(PPh_3)_2$] could catalyze this decarbonylation reaction, although requiring higher temperatures and with lower efficiency (Fig. 1). CO Extrusion from the *trans*-[Rh(CO)Cl$(PPh_3)_2$] at higher temperature (137–144°C) was believed to regenerate the active catalyst $(PPh_3)_2$RhCl. Further screening revealed that 5 mol% $[Rh(cod)Cl]_2$ and 10 mol% $AsPh_3$ would afford **6a** in 68% isolated yield and only trace amounts (2%) of side product **7a**. The electron-deficient nature of $AsPh_3$ may promote reductive elimination, thus explaining the increased selectivity for **6a**. Figure 1 also shows that **4** and **6b** were isolated in 80% and 70% yield, respectively. To obtain **6c** and **6d**, 5 mol% [Rh(cod)dppb]BF_4 was employed as catalyst and provided yields of 99% and 77%, respectively. This decarbonylation reaction constitutes one of the first examples of Rh^I-catalyzed C–C bond activation of cyclobutanones.

Additionally, Murakami and co-workers coupled hydrogenation with C–C bond insertion. Under a hydrogen atmosphere (50 atm), Rh^I-catalyzed C–C bond activation/hydrogenation produced 2-methyl-1,4-butandiol derivatives [28]. Figure 2 summarizes the substrate scope for this reaction. The reaction is compatible with esters and arylhalides, but typically high-pressure hydrogen (50 atm) gas is required for reduction. The yields are generally high except for the substrate with an α-substitution (**9j**).

The reaction was further extended to a cascade sequence by enabling a double C–C bond cleavage reaction (Scheme 2) [29]. Cyclohexenone (**14a**), for example, was successfully isolated in 28% yield when spirocyclobutanone (**10a**) was treated with 5 mol% cationic [Rh(cod)dppe]BF_4 (condition A). The yield was improved to 80% and 89% when using catalysts such as $Rh(dppe)_2Cl$ and $Rh(dppp)_2Cl$, respectively (conditions B and C).

Mechanistically, Murakami and co-workers suggest that Rh^I first inserts into the α C–C bond of the cyclobutanone ring in **10a** via oxidative addition to generate the



Entry	Catalyst	Ligand	Time	Yield[a,b]	
1	*trans*-[Rh(CO)Cl(PPh$_3$)$_2$]	None	23 h	**6a**[a] 17%	**7a**[a] 6%
2	*trans*-[Rh(CO)Cl(PPh$_3$)$_2$]	None	5 d	**6a**[a] 40%	**7a**[a] 22%
3	[Rh(cod)dppb]BF$_4$	None	1 d	**6a**[a] 36%	**7a**[a] 32%
4	[Rh(cod)Cl]$_2$	AsPh$_3$	7 d	**6a**[b] 68%	**7a**[b] 2%

[a] GC yield. [b] Isolated yield.

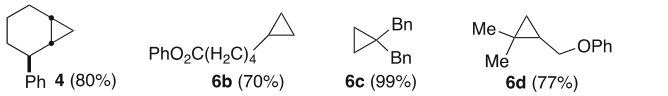
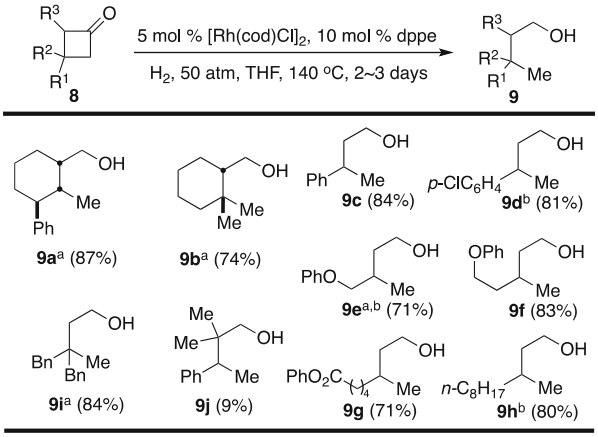


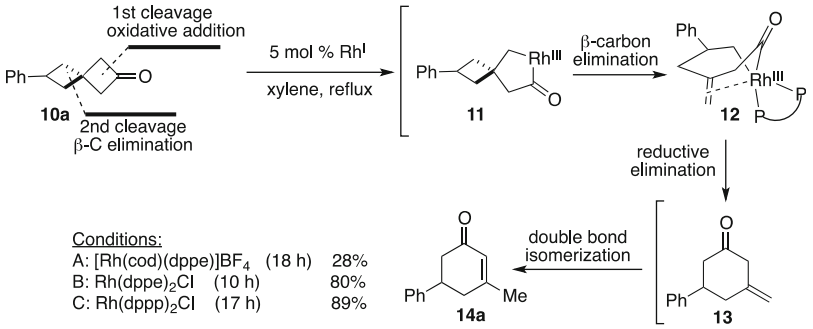
Fig. 1 Catalytic decarbonylation of cyclobutanones



[a] Toluene was used as solvent. [b] After hydrogenolysis, reaction mixture was treated with NaBH$_4$.

Fig. 2 Rh-catalyzed C–C activation/hydrogenation cascade

five-membered rhodacycle (**11**), which subsequently proceeds via β-C elimination to afford seven-membered rhodacycle **12**. Reductive elimination and double bond isomerization furnished cyclohexenone (**14a**). The authors believe strain release of the spiro four-membered ring provide a significant driving force for the reaction and is applicable to a variety of other three or four-membered spirocyclic cyclobutanones (Fig. 3). In substrates with nonequivalent C–C bonds, β-C elimination at the less sterically hindered C–C bond is favored, as demonstrated by substrates **10d** and **10e** in Fig. 3.



Scheme 2 Rh-catalyzed successive C–C bond cleavage

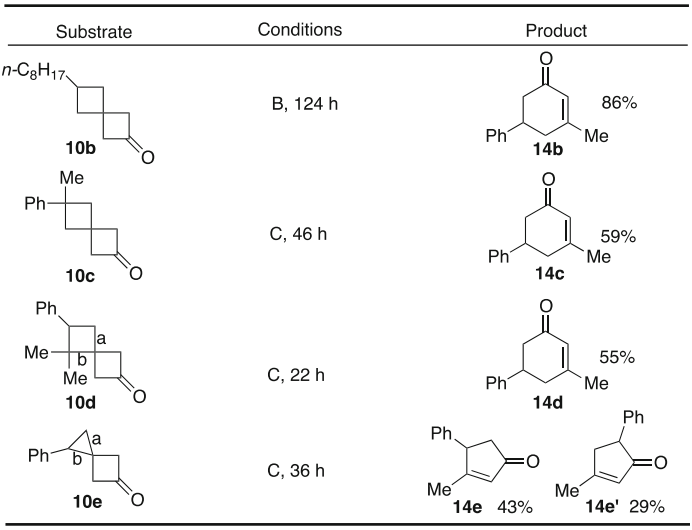
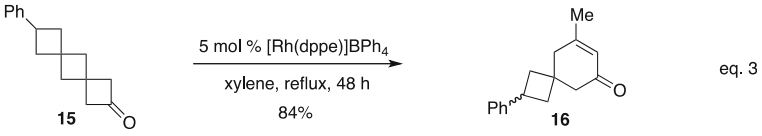


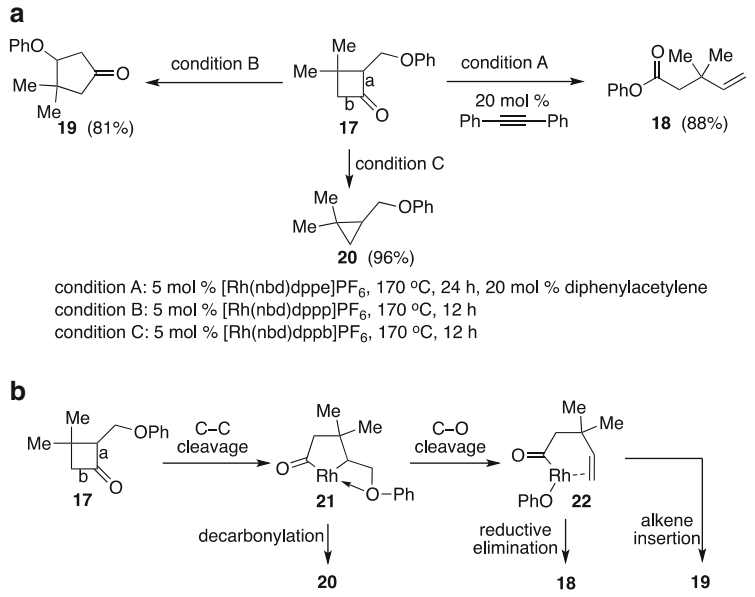
Fig. 3 Substrate scope for successive C–C bond cleavage



Scheme 3 Double C–C bond cleavage

A triple C–C bond cleavage cascade was also attempted (Scheme 3) under the optimized conditions described below with compound **15**; however, only double C–C activation was observed, giving cyclohexenone **16** as the sole product.

A sequential C–C bond activation/C–O bond cleavage reaction was subsequently reported by the same group [30]. It was discovered that alternative reaction

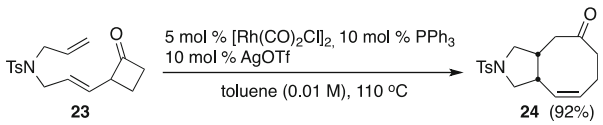


Scheme 4 Rh-catalyzed C–C bond activation/C–O bond cleavage cascade

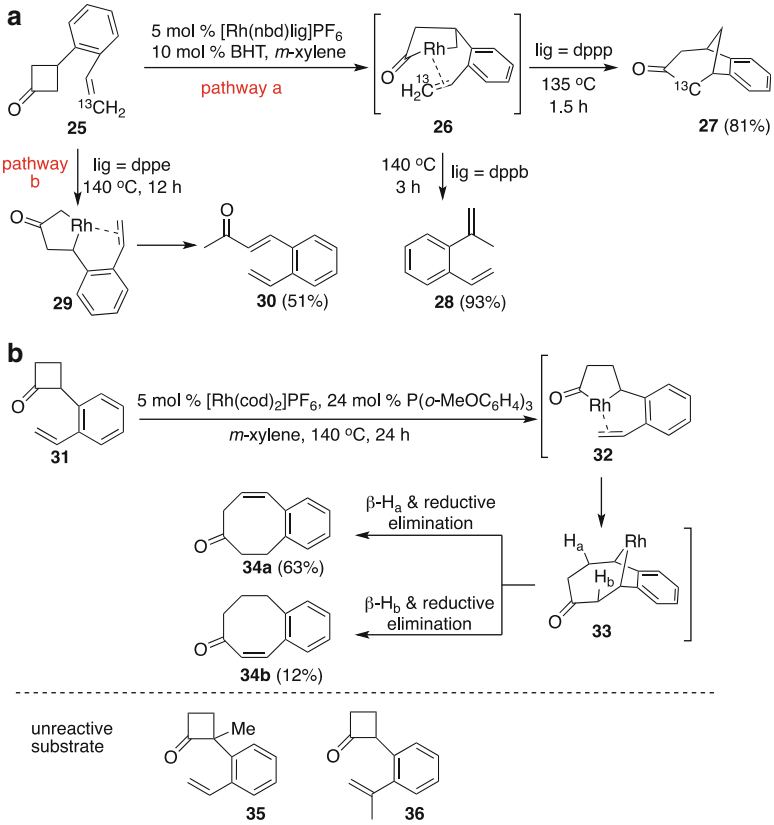
pathways are possible with different bidentate ligands (Scheme 4a). While two possible C–C bonds in cyclobutanone **17** can be activated, Murakami and co-workers suggested bond "a" would preferably undergo C–C bond activation resulting from the directing ability of the benzylic ether. Alternatively cleavage of bond "b" followed by decarbonylation and CO reinsertion can give the same intermediate **21**. The ether (–OPh) directing effects apparently do not govern the reaction, as cyclopentanone **19** was the predominant product (condition B in Scheme 4a). Cleavage of bond "a" can be induced by addition of diphenylacetylene to produce ester **18** (condition A in Scheme 4a). Presumably coordination of the diphenylacetylene competes with the olefin in intermediate **22** to prevent OPh reinsertion, thus favoring reductive elimination to produce **18**. Also, the decarbonylation product cyclopropane **20** could be achieved if a ligand with a large bite angle, such as dppb, was employed (condition C in Scheme 4a).

In 2000, inspired by the work of Liebeskind [31], Wender and co-workers reported [32] an intramolecular Rh-catalyzed [6+2] cycloaddition reaction between vinylcyclobutanone and terminal alkenes (Scheme 5). In this transformation 5 mol% $[Rh(CO)_2Cl]_2$, 10 mol% PPh_3, and 10 mol% AgOTf were employed and cyclooctenone **24** was afforded in 92% yield as a single diastereoisomer. Besides sulfonamides, other linkers such as ether and geminal diesters were also found to be compatible with this reaction condition using specified catalyst precursors.

In 2002, Murakami and co-workers reported [33] that they successfully trapped the five-membered rhodacycle **26** (Scheme 6a) intramolecularly with an alkene to afford benzocyclo[3.2.1]octanone **27**. The ^{13}C-labeled substrate **25** strongly



Scheme 5 Rh-catalyzed [6+2] cycloaddition via C–C bond activation

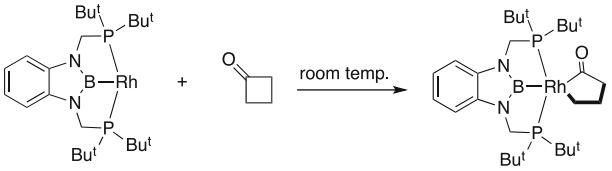


Scheme 6 Rh-catalyzed intramolecular cyclobutanone-alkene coupling

supports "pathway a" where the alkene inserts into the α C–C bond of the cyclobutanone with [Rh(nbd)dppp]PF_6 as catalyst. The reaction outcome significantly depends on the ligand used, as switching from dppp to dppb or dppf gave completely different products. Decarbonylation was observed with dppb to give **28**. It is proposed that the wider bite angle with cationic Rh favors a four-membered rhodacycle as a result of steric repulsion, thus promoting a decarbonylation pathway. With dppe as ligand, the β C–C bond is likely cleaved (**29**) (pathway b) which after β-H elimination and reductive elimination yields **30** in 51% yield. In this

scenario, the alkene presumably serves as a directing group to initiate the C–C cleavage.

The substitution of the cyclobutanone plays an important role in the outcome of the reaction as shown in a later report by Murakami [34]. 2-Substituted cyclobutanone (**31,** Scheme 6b) afforded benzocyclooctenones **34** under the reaction conditions. It was proposed that Rh^I is directed by the terminal olefin to insert into the more hindered α C–C bond, followed by migratory insertion to form intermediate **33**. Non-selective β-H elimination of either H_a or H_b afforded the isomeric mixture of olefins **34a** and **34b**. Further exploration of the substrate scope found that additional steric bulk inhibits the reaction as neither substrate **35** nor **36** reacted.



(2)

Very recently, Matsuda et al. reported [35] a pincer-Rh^I complex that can cleave the α C–C bond of cyclobutanone at room temperature (2). The reactivity is attributed to the highly electron-donating nature of the boron ligand as well as the unsaturated coordination on the rhodium center.

2.2 *Rh-Catalyzed C–C Bond Activation via β-C Elimination*

In addition to direct oxidative addition, β-C elimination is another commonly used strategy to activate C–C bonds (Fig. 4). Utilizing this strategy, Murakami and co-workers reported both racemic and enantioselective C–C activation/C–O forming reactions with phenol-substituted cyclobutanone (**37**) in 2000 [36] and 2007 [37], respectively (Scheme 7a). They propose that the reaction follows a four-step sequence[1] in the catalytic cycle: (1) generation of the rhodium aryloxide **39** (Scheme 7b (i)), (2) nucleophilic addition to the carbonyl group to form rhodium cyclobutanolate **40** (Scheme 7b (ii)), (3) enantioselective β-C elimination to generate **41** (Scheme 7b (iii)), and (4) protonolysis affording **38a** and regenerated catalyst (Scheme 7b (iv)). In the last step, β-H elimination could also take place, thus providing **38b** as the product after isomerization. To further explore the transformation and the proposed mechanism, 2-substituted cyclobutanones **42** and **44** were subjected to the standard conditions (Scheme 7c) to provide seven-membered lactone **43** (β-C elimination with bond "a") and γ-lactone **45** (β-C elimination with bond "b"), respectively.

[1] Murakami suggested an oxidative addition mechanism in [35].

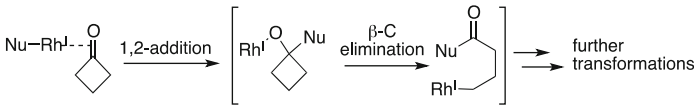
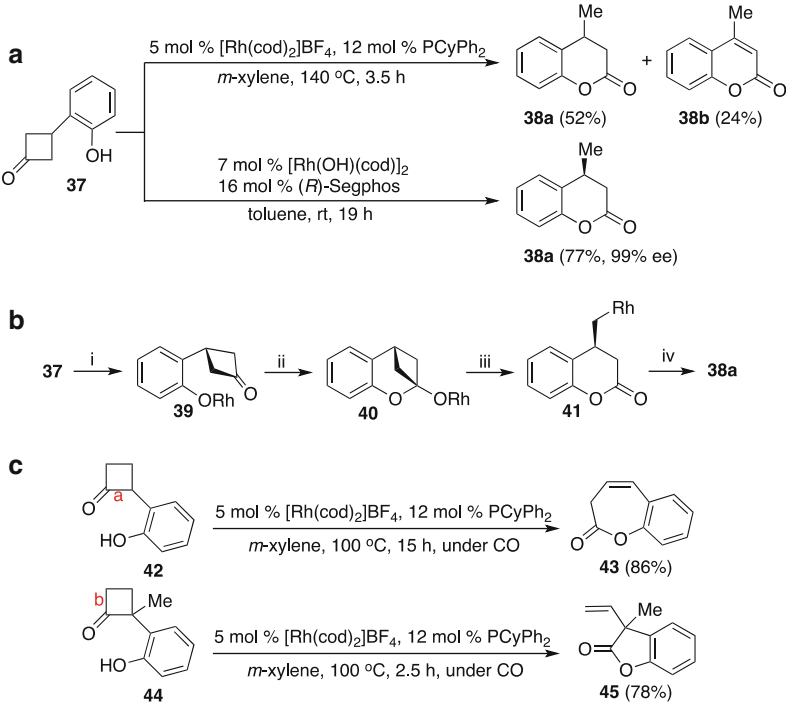
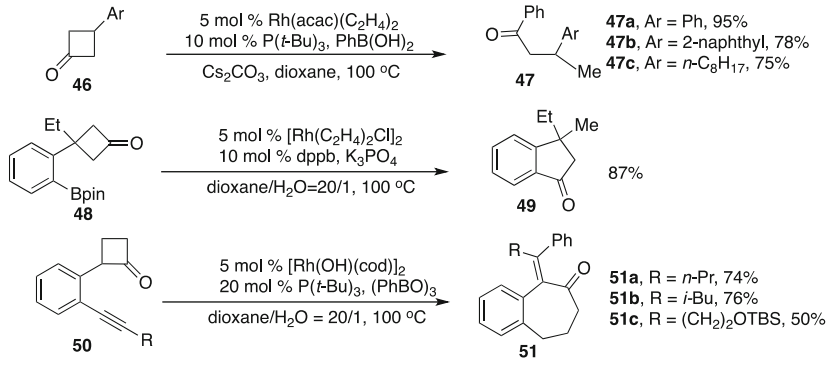


Fig. 4 General C–C activation strategy via β-C elimination



Scheme 7 Rh-catalyzed addition/β-C elimination of cyclobutanones

Besides using Rh-alkoxide as the nucleophile, aryl-Rh species [38–40] have also been demonstrated to add onto cyclobutanone carbonyl groups, following a similar addition/β-C elimination sequence to afford either ring-opening or ring-expansion products (Scheme 8). For example, arylboronic acid/esters undergo transmetallation with Rh^{I}, forming aryl-Rh intermediates, which readily undergo nucleophilic addition into the cyclobutanone moiety, ultimately leading to the products shown. Murakami and co-workers later reported [41, 42] that Pd^{II} could also catalyze this reaction by the analogous mechanistic pathway.



Scheme 8 Aryl-Rh-catalyzed addition/β-C elimination of cyclobutanones

2.3 Ni-Catalyzed C–C Bond Activation via β-C Elimination

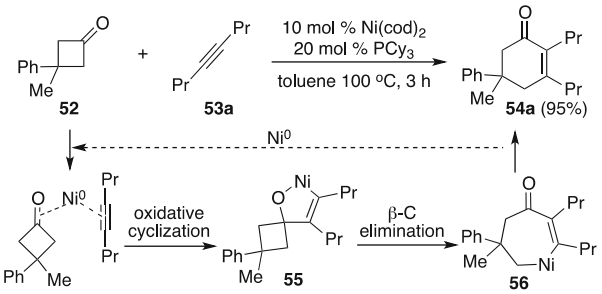
In the arena of C–C bond activation via β-C elimination, Ni shows complementary reactivity to Rh and in fact has unique characteristics: (1) as a first row transition metal, Ni is usually more reactive than its second and/or third row counterparts when cyclometalation [43] is involved; (2) Ni^0-catalyzed aldehyde and alkyne/alkene coupling reactions have been developed [44].

With Ni^0 as a catalyst, an intermolecular [4+2] cycloaddition [45] reaction with cyclobutanone **52** and 4-octyne **53a** produced cyclohexenone **54a** in 95% yield. The proposed reaction mechanism is illustrated in Scheme 9. Presumably the reaction of **52** and **53a** with Ni^0 would proceed through oxidative cyclization to give oxanickelacyclopentene (**55**). β-C elimination cleaves the cyclobutane ring to generate **56** and leads to formation of product **54a** after reductive elimination. Overall, a formal [4+2] cycloaddition was accomplished with Ni^0 via β-C elimination. In contrast, Rh was not an effective catalyst for this transformation.

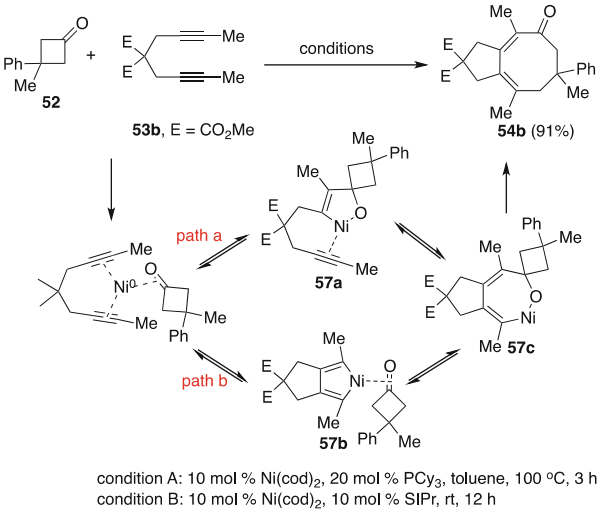
Murakami and co-workers further developed this reaction to a [4+2+2] cycloaddition [46, 47]. Cyclobutanone (**52**) can be effectively coupled with 1,6-diyne (**53b**) to afford bicyclo[6,3,0]undecadienone **54b** in excellent yield (91%). Two possible mechanisms were proposed for this transformation (Scheme 10). Either pathway leads to intermediate **57c**, which upon β-C elimination and reductive elimination of the four-membered ring furnishes the final product.

In addition, the Louie and Aissa groups reported similar transformations by activation of Boc-protected azetidinone (a recent DFT calculation suggests an alternative oxidative addition mechanism for the alkyne insertion into azetidinones [48]) and/or 3-oxetane as the coupling partner [49, 50]. A [4+2] coupling between protected azetidinones and internal alkynes was independently reported by the Louie [51] and Murakami groups [52]. As shown in Scheme 11, protected azetidinone (**58**) and internal alkynes (**59**) can undergo oxidative metallocyclization to afford the sterically more favored intermediate **61b**, which will afford the

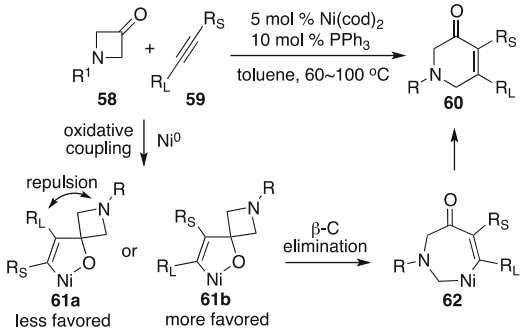
Scheme 9 Formal intermolecular [4+2] cycloaddition catalyzed by Ni^0



Scheme 10 Formal [4+2+2] cycloaddition catalyzed by Ni^0

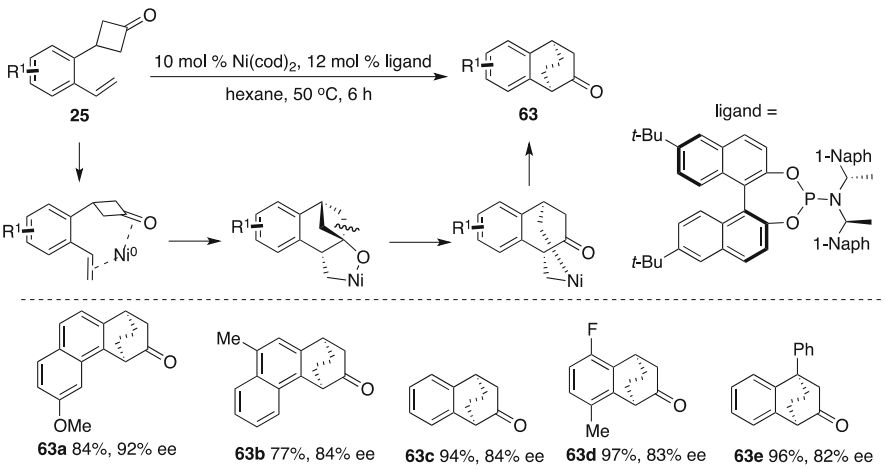


Scheme 11 Ni-catalyzed 3-piperidone synthesis

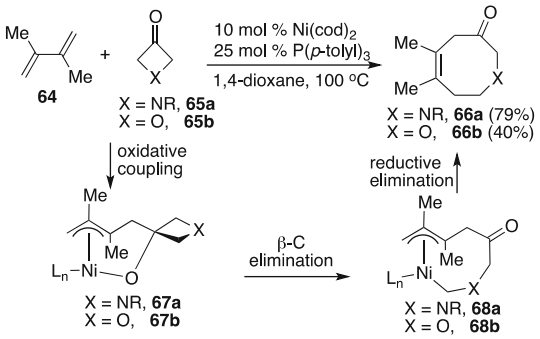


piperidone (**60**) after β-C elimination and reductive elimination. The yield of this reaction ranges from 56% to quantitative.

Besides coupling with alkynes, in 2006 Murakami and co-workers reported [53] a Ni-catalyzed intramolecular coupling of cyclobutanones with alkenes. An asymmetric version of this reaction was reported [54] by the same group in 2012



Scheme 12 Asymmetric carboacylation of olefins catalyzed by Ni^0



Scheme 13 Ni-catalyzed cycloaddition of 1,3-dienes with heterocyclic four-membered ketones

(Scheme 12) (during the preparation of this manuscript, a new asymmetric reaction was reported [55]) [56]. A similar mechanism was proposed and benzobicyclo [2,2,2]octenone **63** was isolated in high yield (77–97%) and ee (80–93%). Thus far, this is a unique example of an intermolecular carboacylation of alkenes via C–C bond activation. One year later, Louie and co-workers reported a nickel-catalyzed cycloaddition of 1,3-dienes with 3-azetidinones and 3-oxetanones [57]. In their report, the combination of $Ni(cod)_2$ and monodentate phosphine P(*p*-tolyl)$_3$ was found to successfully couple 1,3-dienes and 3-azetidinones/3-oxetanones and afford eight-membered heterocycles in medium to good yield. It is interesting to note that only 2,3-substituted dienes were suitable substrates, primarily because of sterics (Scheme 13).

3 C–C Bond Activation of Cyclobutenones

In addition to cyclobutanone-based substrates, their unsaturated counterparts, cyclobutenones also participate in C–C activation transformations (for thermal opening of cyclobutenones, see [58]). Although activation of cyclobutenones follows the same guiding principles (Scheme 1), they can proceed under alternate mechanistic pathways that allow for distinct outcomes and products. Due to their unsymmetrical nature, C–C cleavage reactions with cyclobutenones often have interesting site-selectivity challenges (Fig. 5). Cyclobutenones are considered as vinyl ketene equivalents [58]; thus, cleavage of the C1–C4 bond is generally kinetically favored. However, sp^2 carbon–metal bonds are known to be stronger than sp^3 carbon–metal bonds; thus cleavage of the C1–C2 bond can be thermodynamically preferred. Besides thorough studies of ring openings with stoichiometric transition metals, to date a number of catalytic and synthetically useful transformations have been developed.

3.1 Stoichiometric C–C Bond Activation

Studies towards C–C bond activation of cyclobutenones predated cyclobutanones research with the pioneering work by Liebeskind and co-workers. They found [59, 60] that when cyclobutenone **69** was treated with an equimolar amount of $Rh(PPh_3)_3Cl$, rhodacyclopentenone **70** precipitated from the reaction via cleavage of the C1–C4 bond (Scheme 14). Cyclobutenones containing electron-deficient substituents were more reactive. A single-crystal X-ray structure was obtained for **70d**, which supported the molecular structure of the Rh-complex. The same transformation can also be performed on benzocyclobutenones, e.g., **71**. A mixture of products was observed when the reaction was stopped after 5 h. However, when the reaction was heated for 5 days, activation of the C1–C2 bond (bond "a") was observed as the major product affording a 30/1 ratio of **72b**/**72a**. It was found that **72a** can isomerize to **72b** upon heating at high temperature, suggesting **72a** is the kinetic product (130°C, 6 h). The authors speculated that the methylenedioxyl group in **71** may coordinate to the rhodium, leading to the more thermodynamically preferred product.

While these rhodacycles were found to be inert with alkynes [60], the concept of single C–C bond activation of cyclobutenones and/or benzocyclobutenones using late transition metals was still established. With an attempt to discover more reactive metallacycles, cobalt complex **73** was prepared and used in the stoichiometric C–C bond activation of cyclobutenones (**74**, Scheme 15).

Cobaltacyclopentenone **75a** was successfully obtained when **73** reacted with cyclobutenone **74a**, albeit in low yield, most likely because **74a** is less electrophilic. When a Lewis acid ($ZnCl_2$) was employed to enhance reactivity, a different regioisomeric product (**75b**) was observed. The proposed rationale involves a

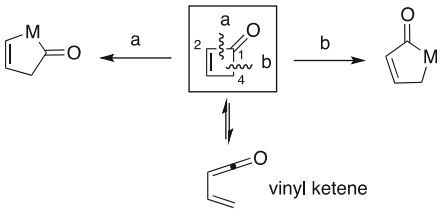
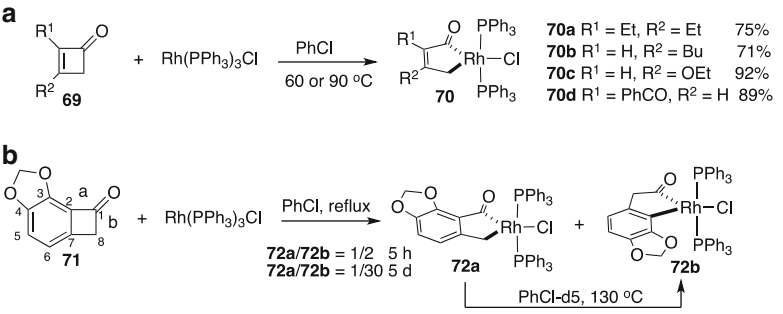
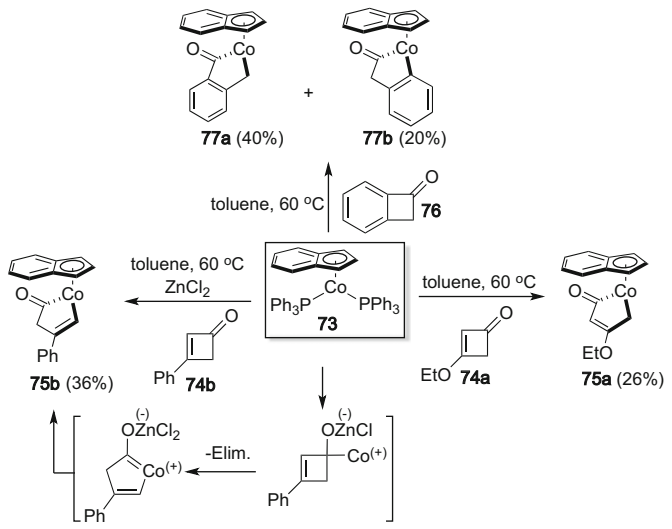


Fig. 5 General strategy of C–C activation using cyclobutenone



Scheme 14 Rh-mediated stoichiometric C–C bond activation of cyclobutenones/benzocyclobutenones



Scheme 15 Co^{I} complex-mediated C–C bond activation of cyclobutenone

stepwise C–C bond cleavage mechanism, wherein $ZnCl_2$ activation of **73** leads to cobalt nucleophilic attack at the carbonyl, followed by an α-C elimination and isomerization to afford metallacycle **75b**. When benzocyclobutenones were used as substrates both C–C bond cleaved products were observed; however, no isomerization of **77a** to **77b** was observed, even under harsher conditions.

3.2 Rh-Catalyzed C–C Bond Activation of Cyclobutenones

Liebeskind and co-workers showed that stoichiometric cobaltacyclopentenone species [61] could react with alkynes to furnish phenol derivatives, and later a Ni-catalyzed transformation was developed [62] (Fig. 6). The reaction shows less regioselectivity in alkyne insertion for internal unsymmetrical alkyne substrates.

C–C bond activation of cyclobutenones followed by ring expansion via β-C elimination cascade serves as a unique strategy to form medium-sized rings. Liebeskind and co-workers designed [31] a double C–C bond cleavage reaction of cyclopropyl-substituted cyclobutenones to product seven-membered rings. When substrate **78** was treated with 5 mol% $Rh(PPh_3)_3Cl$, cycloheptadienone **79** and its isomer **79′** were isolated in satisfactory yields (Scheme 16a). This method was also extended (Scheme 16b) to cyclobutyl-substituted substrate **82** where cyclooctadienone **83** was obtained in 90% yield.

Other catalytic transformations involving C–C bond activation of cyclobutenones have also been developed. For example, Kondo and co-workers reported [63, 64] an Rh-catalyzed dimerization of cyclobutenone **84** to form pyranones **85** (Scheme 17). Furthermore, they demonstrated that the rhodacyclopentenone intermediate can be trapped with reactive alkenes, such as norbornene, to give decarbonylation product **86** or direct insertion product **87**.

In 2012, Xu and Dong reported [65] the Rh-catalyzed intramolecular carboacylation between benzocyclobutenones (**88**) and olefins (Scheme 18). One unique feature is that the olefin inserts into the C1–C2 bond instead of the more reactive C1–C8 bond. They propose the olefin serves as both a directing group and trapping reagent for the C–C bond cleavage intermediate **89**. Through migratory insertion followed by reductive elimination, a tricyclic fused-ring compound **90** was furnished from this transformation, a core structure found in many natural products (Scheme 18). This racemic transformation was optimized with dppb as the bidentate phosphine ligand. The relatively large bite angle was attributed to facilitate this reaction. This "cut and sew" transformation can enable insertion of various olefins, including mono-, di-, and even tri-substituted alkenes with both alkyl and aromatic substituents. They also discovered that addition of a Lewis acid, such as $ZnCl_2$, as a co-catalyst can enhance the overall reactivity and can enable one to include more challenging substrates, such as tri-substituted alkenes (**90g**) and those that form hydropyran rings (**90e**). The asymmetric version of this transformation was developed later by the same group using (*R*)-dtbm-segphos as the chiral ligand and produced tricyclic ring scaffold **90** in 92–99% ee [66].

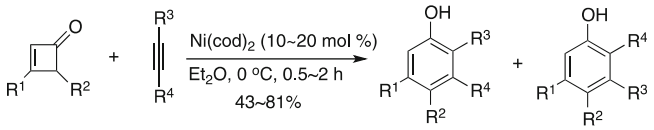
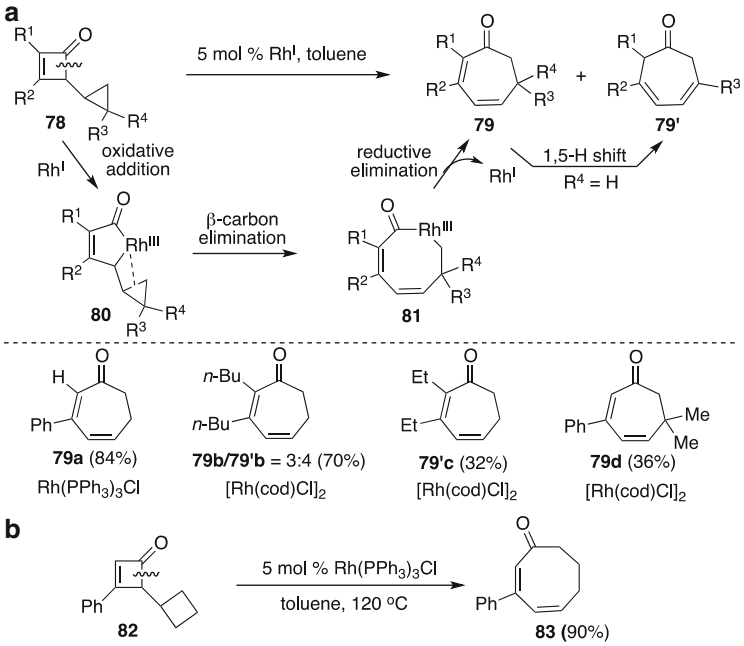
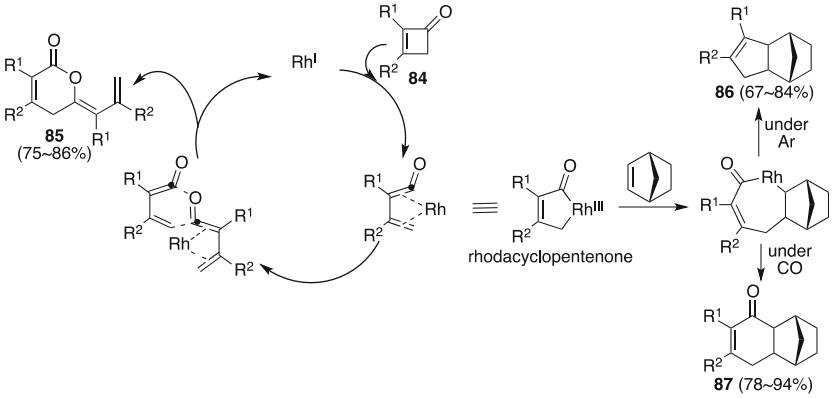


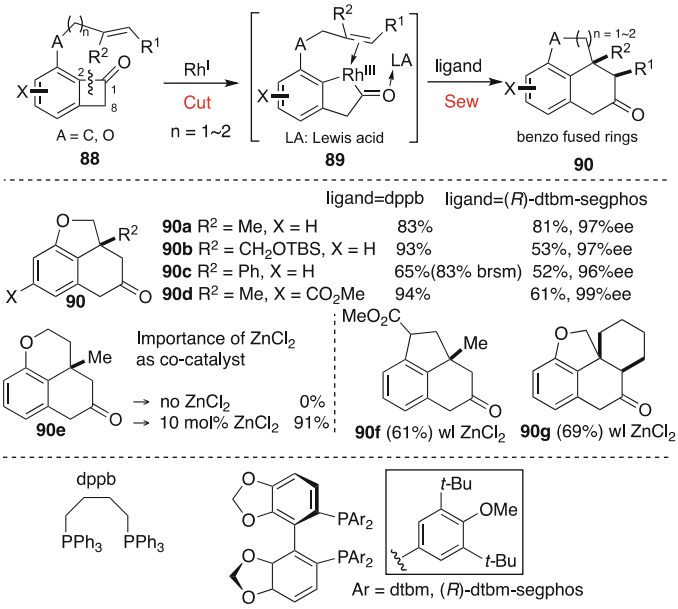
Fig. 6 Ni-catalyzed cyclobutenone-alkyne couplings



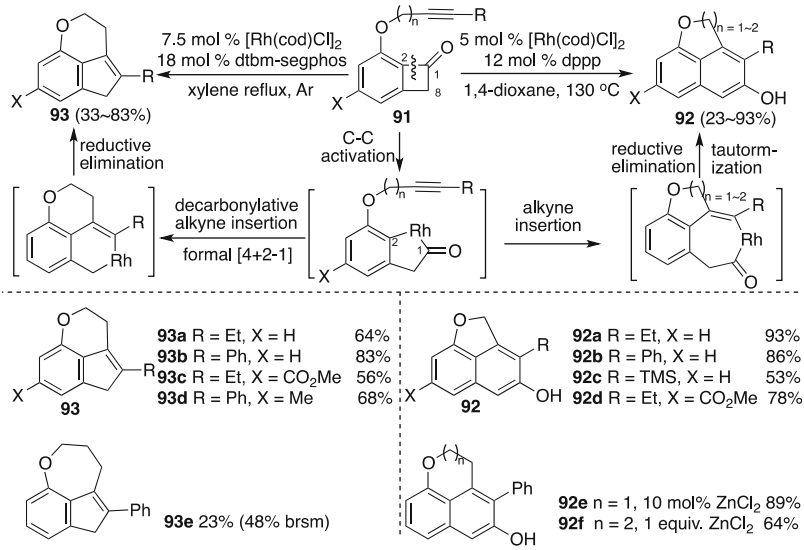
Scheme 16 Rh-catalyzed C–C bond activation to make medium-sized rings



Scheme 17 Intermolecular norbornene insertion via C–C bond activation

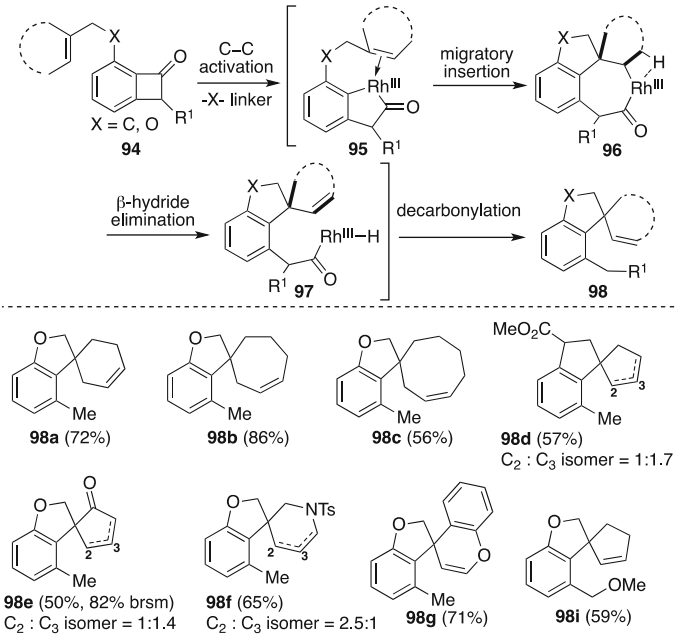


Scheme 18 Rh-catalyzed carboacylation of olefins via C–C bond activation



Scheme 19 Rh-catalyzed intramolecular alkyne insertion via C–C bond activation

Catalytic intramolecular alkyne insertions into benzocyclobutenones were also recently developed [67] by Dong and co-workers (Scheme 19). Besides selectively forming the normal "cut and sew" product **92** (β-naphthols), the decarbonylative



Scheme 20 Rh-catalyzed multi-substituted olefin insertion featuring C–C activation/β-H elimination sequence to produce spirocyclic rings

insertion product (**93**) became the dominating product by switching to slightly different reaction conditions. While the reason is still unclear, dtbm-segphos ligand gave the highest selectivity for decarbonylation products. With this divergent strategy, a variety of fused β-naphthol and indene scaffolds could be obtained in good yields with high functional group tolerance.

Spirocyclic rings are commonly found in a variety of natural products, yet efficient methods to build these structural motifs with high functional group compatibility are limited. Very recently, Xu, Savage, and Dong reported [68], a Rh-catalyzed spirocyclization, via C–C bond activation of benzocyclobutenone **94** that contains a tri-substituted cyclic olefin. $[Rh(CO)_2Cl]_2$ (5 mol%) with tris (pentafluorophenyl)phosphine $[P(C_6F_5)_3]$ (10 mol%) was identified as an excellent catalytic system to carry out this transformation (Scheme 20). The electron-deficient nature of $P(C_6F_5)_3$ is the key to assisting rhodacycle **95** to insert into the sterically hindered poly-substituted olefins, which, upon β-H elimination and decarbonylation, leads to spirocycle products. Selective olefin chain walk was observed for a number of substrates (e.g. **98a–c**) whereas the cause for such selectivity is unclear. Substrates containing various ring sizes can undergo decarbonylative spirocyclization. In addition, many sensitive functional groups, such as dienes, ketones, enamides, esters, benzyl and vinyl ethers, and unprotected tertiary alcohols, are all compatible.

4 C–C Bond Activation of Cyclobutenediones

While several different substrates have been presented thus far, cyclobutenediones were among the first four-membered cyclic ketone substrates studied for C–C bond activation, primarily due to the combination of high strain energy, relative stability, and ready availability. The first report of cyclobutenedione C–C bond cleavage was published in 1973, when Kemmitt and co-workers found [69, 70] that benzocyclobutenedione (**99**) could react with $Pt(PPh_3)_4$ at even ambient temperature to afford platinumcyclopentadione (**100**) as red crystals (Scheme 21). Cyclobutenediones are also suitable substrates. This stoichiometric study was at the forefront of C–C bond activation of cyclobutenediones and benzocyclobutenediones.

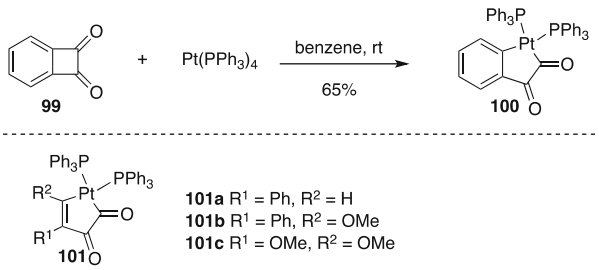
4.1 Stoichiometric C–C Bond Activation of Cyclobutenediones

Kemmitt and co-workers' pioneering work using $Pt(PPh_3)_4$ to effect the C–C bond cleavage of cyclobutenediones led to further developments with other transition metals [71–81]. In the 1980s, Liebeskind and co-workers found [71, 72] that when benzocyclobutenedione **99** was treated with $Rh(PPh_3)_3Cl$, $Co(PPh_3)_3Cl$ or $Fe(CO)_5$, metallacyclopentadiones **102** could be isolated in satisfactory yields (Scheme 22). In the case of rhodium, a kinetic product similar to **101** was detected initially, which most likely isomerizes slowly to the thermodynamically favored product **102**.

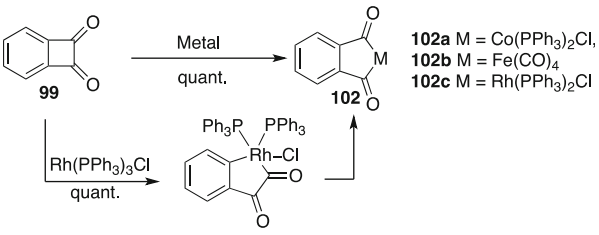
The phthaloylmetal (**102**) species can serve as a reactive four-atom precursor for the synthesis of 1,4-quinones [73–81]. Liebeskind and co-workers extensively investigated these intermediates, especially a phthaloylcobalt complex (**102a**). They observed that the reactions of **102a** with alkynes were extremely sluggish; however, addition of 2 equiv. of silver salt boosted the reactivity to provide 1,4-benzoquinone products in moderate to high yields [78]. The development of the methodology led to a total synthesis of nanaomycin A [77] (Scheme 23). Furthermore, mechanistic studies revealed that additional PPh_3 ligand decreased the reaction rate; dimethylglyoxime was found to be a more suitable ligand, which stabilized the phthaloylcobalt species while maintaining the reactivity with alkynes.

4.2 Catalytic C–C Bond Activation of Cyclobutenediones

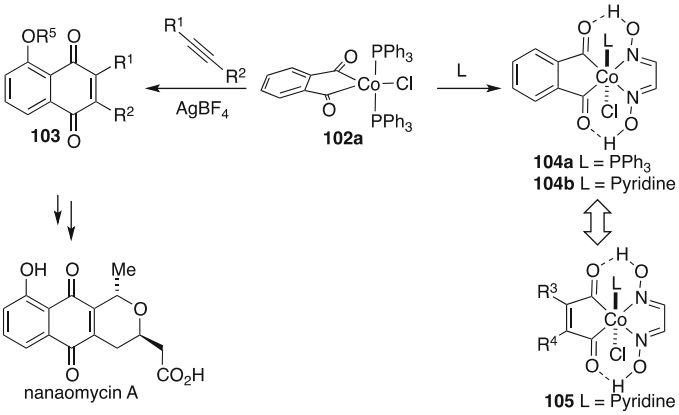
In 2000, Mitsudo and co-workers reported the first example of catalytic C–C bond activation/olefin insertion of cyclobutenediones [82, 83] using $Ru_3(CO)_{12}$ as the catalyst (Scheme 24). The authors proposed that $Ru_3(CO)_{12}$ inserts into bond "b" similar to $Pt(PPh_3)_4$ insertion (Scheme 21), after which decarbonylation and insertion into norbornene yields cyclopentenone **107**. When ^{13}CO was used, the



Scheme 21 Pt-mediated stoichiometric C–C bond activation



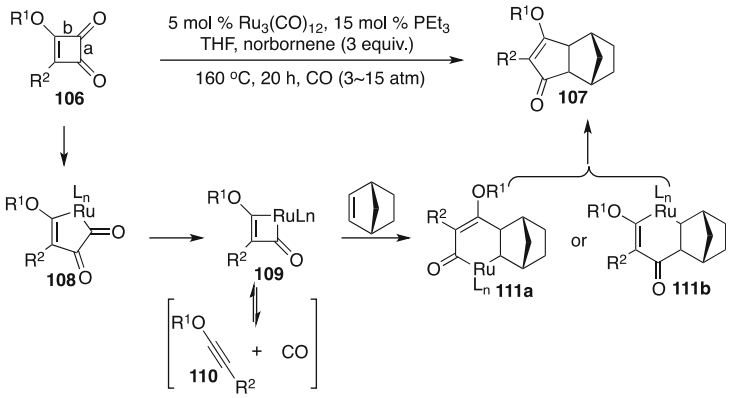
Scheme 22 Activation of benzocyclobutenediones with Fe, Co, and Rh



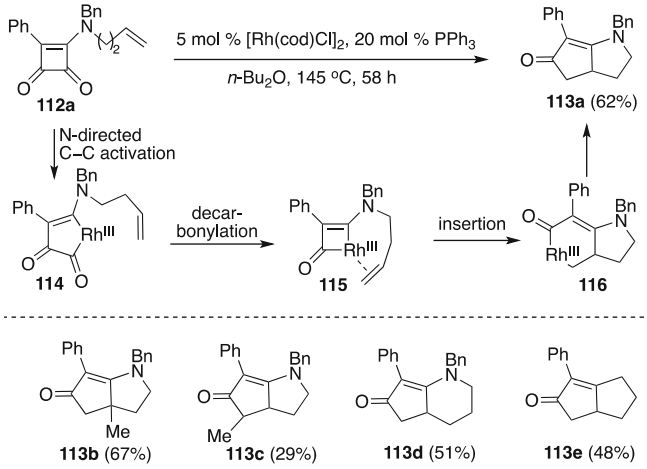
Scheme 23 Total synthesis of nanaomycin A featuring C–C bond activation

^{13}C-labeled **107** was observed in 70% yield. The authors suggested an equilibration between the decarbonylated rhodacycle **109** and its disassembled form **110**, although CO exchange with complex **111a** is also possible. In addition, under high CO pressure (50 atm), the decarbonylation was suppressed and the direct norbornene-insertion product, hydroquinones, was isolated as the major product.

An intramolecular decarbonylative alkene insertion into cyclobutenediones to give azabicycloalkenones **113** was reported by Yamamoto [84]. The authors found



Scheme 24 Intermolecular decarbonylative carboacylation of norbornene



Scheme 25 Rh-catalyzed intramolecular decarbonylative carboacylation

that the in situ generated Wilkinson's catalyst provided optimal results. An analogous mechanism involving C–C bond cleavage, decarbonylation, alkene migratory insertion, and reductive elimination, was proposed (Scheme 25). The nitrogen-linkage was not necessary as the methylene-mediated substrate also provided the desired product (**113e**).

5 Conclusion

While still in a developing stage, transition metal-catalyzed C–C bond activation of four-membered ring ketones has emerged as a useful synthetic methodology to enable transformations that are difficult via conventional approaches. Given that most of these four-membered ring ketones can be readily accessed, these methods provide new strategies to prepare various ring systems from relatively simple starting materials. Thus, these advancements allow for C–C bonds to be treated as a useful functional group rather than an inert bond with little synthetic value. Clearly, limitations still exist with most of these methods, such as needs of high reaction temperature, high catalyst loading and substrate restraints; consequently, few practical applications have been demonstrated to date. We expect future research in this field will likely focus on development of more efficient catalytic systems and reliable transformations with broad substrate scope and functional group tolerance while making their applications in complex molecule synthesis more practical.

Acknowledgement We thank UT Austin and CPRIT for a startup fund, NIGMS (R01GM109054-01) and the Welch Foundation (F 1781) for research grants. We thank Prof. Yoshiaki Nakao for proofreading this review chapter and thoughtful suggestions, and we also thank Dr. Jotham W. Coe for his generous efforts in editing the manuscript.

References

1. Trost BM (1991) Science 254:1471–1477
2. Corey EJ, Cheng X-M (2009) The logic of chemical synthesis. Wiley-VCH, Weinheim
3. Nicolaou KC, Sorensen EJ (1996) Classics in total synthesis: targets, strategies, methods. Wiley-VCH, Weinheim
4. Nicolaou KC, Snyder SA (2003) Classics in total synthesis II: more targets, strategies, methods. Wiley-VCH, Weinheim
5. Nicolaou KC, Chen J (2011) Classics in total synthesis III. Wiley-VCH, Weinheim
6. Yu J-Q, Shi Z-J (eds) (2010) C–H activation. Springer, Berlin, Heidelberg
7. Winter C, Krause N (2009) Angew Chem Int Ed 48:2460–2462
8. Najera C, Snasano JM (2009) Angew Chem Int Ed 48:2452–2456
9. Seiser T, Cramer N (2009) Org Biomol Chem 7:2835–2840
10. Rybichinski B, Milstein D (1999) Angew Chem Int Ed 38:870–883
11. Jun C-H (2004) Chem Soc Rev 33:610–618
12. Murakami M, Ito Y (1999) Top Organomet Chem 3:97–129
13. Perthuisot C, Edelbach BJ, Zubirs DL, Simhai H, Iverson CN, Muller C, Satoh T, Jones WD (2002) J Mol Catal A 189:157–168
14. Ruhland K (2012) Eur J Org Chem 14:2683–2706
15. Ruben M, Rubina M, Gevorgyan V (2007) Chem Rev 107:3117–3179
16. Seiser T, Saget T, Tran DN, Cramer N (2011) Angew Chem Int Ed 50:7740–7752
17. Tipper CFH (1955) J Chem Soc 2045–2046
18. Cassar L, Eaton PE, Halper J (1970) J Am Chem Soc 92:6366–6368
19. Bishop KC (1976) Chem Rev 76:461–486

20. Crabtree RH, Dion RP (1984) J Chem Soc Chem Commun 1260–1261
21. Suggs JW, Jun CH (1984) J Am Chem Soc 106:3054–3056
22. Liebeskind LS, Baysdon SL, South MS, Lyer S (1985) Tetrahedron 41:5839–5853
23. Periana RA, Bergman RG (1986) J Am Chem Soc 108:1346–7355
24. Hartwig JF, Andersen RA, Bergman RG (1989) J Am Chem Soc 111:2717–2719
25. Gozin M, Wesman A, Ben-David Y, Milstein D (1993) Nature 364:699–701
26. Murakami M, Amii H, Ito Y (1994) Nature 370:540–541
27. Rusina A, Vlcek A (1965) Nature 206:295–296
28. Murakami M, Amii H, Shigeto K, Ito Y (1996) J Am Chem Soc 118:8285–8290
29. Murakami M, Takahashi K, Amii H, Ito Y (1997) J Am Chem Soc 119:9307–9308
30. Murakami M, Takahashi T, Amii H, Ito Y (1998) J Am Chem Soc 120:9949–9950
31. Huffman MA, Liebeskind LS (1993) J Am Chem Soc 115:4895–4896
32. Wender PA, Correa AG, Sato Y, Sun R (2000) J Am Chem Soc 122:7815–7816
33. Murakami A, Itahashi T, Ito Y (2002) J Am Chem Soc 124:13976–13977
34. Matsuda T, Fujimoto A, Ishibashi M, Murakami M (2004) Chem Lett 33:876–877
35. Masuda Y, Hasegawa M, Yamashita M, Nozaki K, Ishida N, Murakami M (2013) J Am Chem Soc 135:7142–7145
36. Murakami M, Tsuruta T, Ito Y (2000) Angew Chem Int Ed 39:2484–2486
37. Matsuda T, Shigeno M, Murakami M (2007) J Am Chem Soc 129:12086–12087
38. Matsuda T, Makino M, Murakami M (2004) Org Lett 6:1257–1259
39. Matsuda T, Shigeno M, Makino M, Murakami M (2006) Org Lett 8:3379–3381
40. Matsuda T, Makino M, Murakami M (2004) Angew Chem Int Ed 44:4608–4611
41. Matsuda T, Shigeno M, Murakami M (2008) Org Lett 10:5219–5221
42. Ishida N, Ikemoto W, Murakami M (2012) Org Lett 14:3230–3232
43. Montgomery J (2013) Organonickel chemistry. In: Organometallics in synthesis: fourth manual. Wiley, Hoboken, pp 319–428
44. Oblinger E, Montgomery J (1997) J Am Chem Soc 119:9065–9066
45. Murakami M, Ashida S, Matsuda T (2005) J Am Chem Soc 127:6932–6933
46. Murakami M, Ashida S, Matsuda T (2006) J Am Chem Soc 128:2166–2167
47. Ashida S, Murakami M (2008) Bull Chem Soc Jpn 81:885–893
48. Li Y, Lin Z (2013) Organometallics 32:3003–3011
49. Kumar P, Zhang K, Louie J (2012) Angew Chem Int Ed 51:8602–8606
50. Ho KYT, Aissa C (2012) Chem Eur J 18:3486–3489
51. Kumar P, Louie J (2012) Org Lett 14:2026–2029
52. Ishida N, Yuhki T, Murakami M (2012) Org Lett 14:3898–3901
53. Murakami M, Ashida S (2006) Chem Commun 4599–4601
54. Liu L, Ishida N, Murakami M (2012) Angew Chem Int Ed 51:2485–2488
55. Parker E, Cramer N (2014) Organometallics 33:780–787
56. Souillart L, Parker E, Cramer N (2014) Angew Chem Int Ed 53:3001–3005
57. Thankur A, Facer ME, Louie J (2013) Angew Chem Int Ed 52:12161–12165
58. Danheiser RL, Gee SK (1984) J Org Chem 49:1672–1674
59. Huffman MA, Liebeskind LS (1990) Organometallics 9:2194–2196
60. Huffman MA, Liebeskind LS (1992) Organometallics 11:255–266
61. Huffman MA, Liebeskind LS (1990) J Am Chem Soc 112:8617–8618
62. Huffman MA, Liebeskind LS (1991) J Am Chem Soc 113:2771–2772
63. Kondo T, Tagushi Y, Kaneko Y, Niimi M, Mitsudo T (2004) Angew Chem Int Ed 43:5369–5372
64. Kondo T, Miimi M, Nomura M, Wada K, Mitsudo T (2007) Tetrahedron Lett 48:2837–2839
65. Xu T, Dong G (2012) Angew Chem Int Ed 51:7567–7571
66. Xu T, Ko HM, Savage NA, Dong G (2012) J Am Chem Soc 134:20005–20008
67. Chen P, Xu T, Dong G (2013) Angew Chem Int Ed 53:1674–1678
68. Xu T, Savage NA, Dong G (2013) Angew Chem Int Ed 53:1891–1895

69. Evans JA, Everitt GF, Kemmitt RDW, Russell DR (1973) J Chem Soc Chem Commun 158–159
70. Hamner ER, Kemmitt RDW, Smith MA (1974) J Chem Soc Chem Commun 841–842
71. Liebeskind LS, Baysdon SL, South MS, Blount JF (1980) J Organomet Chem 202:C73–C76
72. Liebeskind LS, Baysdon SL, South MS (1980) J Am Chem Soc 102:7398–7400
73. Baysdon SL, Liebeskind LS (1982) Organometallics 1:771–775
74. Liebeskind LS, Leeds JP, Baysdon SL, Iyer S (1984) J Am Chem Soc 106:6451–6453
75. Jewell CF Jr, Liebeskind LS, Williamson M (1985) J Am Chem Soc 107:6715–6716
76. Iyer S, Liebeskind LS (1987) J Am Chem Soc 109:2759–2770
77. South MS, Liebeskind LS (1984) J Am Chem Soc 106:4181–4185
78. Liebeskind LS, Baysdon SL, Goedken V, Chidambaram R (1986) Organometallics 5:1086–1092
79. Cho SH, Wirtz KR, Liebeskind LS (1990) Organometallics 9:3067–3072
80. Liebeskind LS, Chidambaram R (1987) J Am Chem Soc 109:5025–5026
81. Hoberg H, Herrera A (1981) Angew Chem Int Ed 20:876–877
82. Kondo T, Nakamura A, Okada T, Suzuki N, Wada K, Mitsudo T (2000) J Am Chem Soc 122:6319–6320
83. Mitsudo T, Kondo T (2001) Synlett 309–321
84. Yamamoto Y, Kuwabara S, Hayashi H, Nishiyama H (2006) Adv Synth Catal 348:2493–2500