CHEMICAL REVIEWS

Review

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Recent Methodologies That Exploit C−C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes

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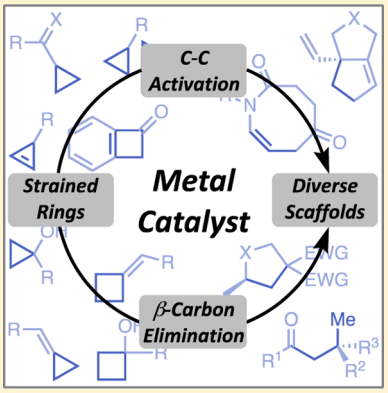
ABSTRACT: In this review, synthetic and mechanistic aspects of key methodologies that exploit C−C single-bond cleavage of strained ring systems are highlighted. The focus is on transition-metal-catalyzed processes that are triggered by C−C bond activation and β-carbon elimination, with the review concentrating on developments from mid-2009 to mid-2016.



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1. INTRODUCTION

Small (three- and four-membered) saturated and unsaturated rings are ideal candidates for metal-catalyzed C−C bond cleavage methodologies. The strain-release energy associated with the cleavage event provides a major driving force, with the resulting organometallic intermediate offering access to a range of mechanistic pathways. Because the activation step is reagent-free, such reaction manifolds automatically provide highly atom-economical processes, thereby fulfilling a key ideal of modern synthetic chemistry.[1,2] Oxidative addition of metals into C−C bonds, termed C−C bond activation, can be achieved by undirected or directed approaches, with the latter often enhancing reaction rates and/or offering increased regiocontrol (Scheme 1A). β-Carbon elimination pathways provide a complementary method to achieve C−C cleavage, allowing activation of less reactive C−C bonds. In this approach, the process is necessarily directed and the metal does not change oxidation state (Scheme 1B).

The purpose of this review is to highlight key methodologies involving strained ring systems that exploit these C−C single-bond cleavage mechanisms. This area has developed rapidly in recent years, and this review concentrates on key synthetic advances reported from mid-2009 to mid-2016; earlier developments involving strained[3−5] and nonstrained C−C bonds have been reviewed.[6] Recent books also provide in-depth discussion of processes underpinned by C−C bond cleavage.[7,8] The focus here is on the range of ring systems that can be used and key mechanistic features that underpin the methodologies. The review is not designed to provide a comprehensive historical account of all developments in the field. For in-depth discussion of a particular area, the reader is directed to recent review articles at the appropriate point.

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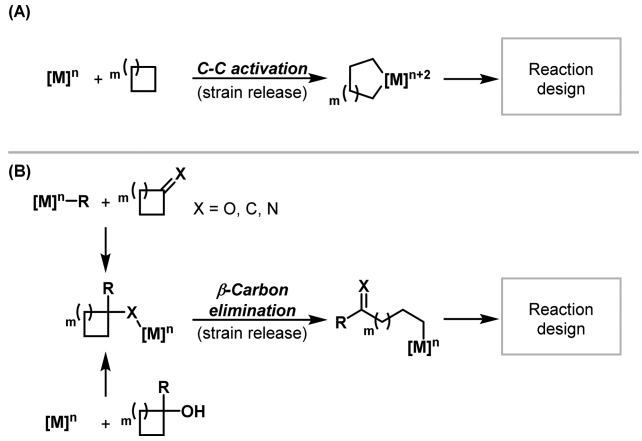
Scheme 1. C−C Cleavage of Small Rings by (A) C−C Activation and (B) β-Carbon Elimination



2. C−C OXIDATIVE ADDITION-BASED METHODOLOGIES

The oxidative addition of transition metals into strained C−C bonds is a well-established process.[9] Indeed, as early as 1955, Tipper[10] reported the insertion of $PtCl_2$ into cyclopropane to generate a platinacyclobutane. Cyclopropane-based ring systems have thus emerged as key initiating motifs in C−C activation methodologies (Figure 1). The introduction of

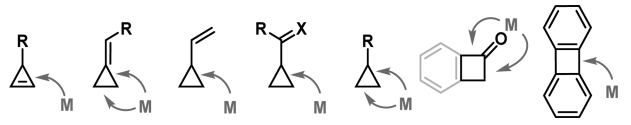


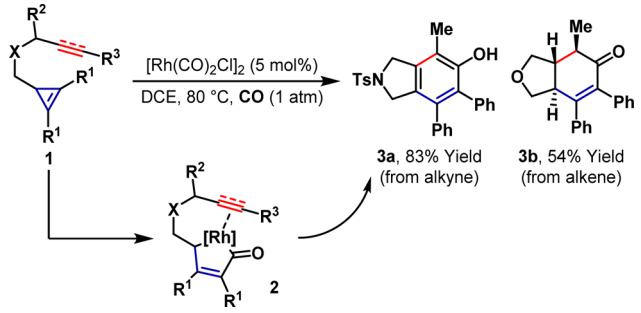
Figure 1. Small ring systems used in recent C−C bond activation methodologies and common sites for metal insertion.

trigonal centers onto cyclopropanes has long been known to result in a significant increase in ring strain.[11−13] As such, recent C−C activation methodologies have exploited cyclopropenes and alkylidenecyclopropanes. Other commonly employed classes of activated cyclopropane include vinylcyclopropanes and cyclopropyl ketones/imines. Processes involving non-activated cyclopropanes are much rarer but have started to emerge. Methodologies based on activation of four-membered rings have also been reported, with significant developments in catalysis based on metal insertion into cyclobutanones and benzocyclobutenones. Biphenylenes, which are classic substrates for C−C bond activation, have also underpinned important recent methodologies.

2.1. Cyclopropene-based Processes

Cyclopropane-based systems possessing internal or fused unsaturation are highly susceptible to cleavage by transition metals.[14−16] However, despite this, processes involving cyclopropenes are rare, perhaps due to the lack of flexibility in substrate synthesis. In 2010, Wang and co-workers[17] reported Rh-catalyzed carbonylative (3 + 1 + 2) cycloadditions of cyclopropenes with tethered alkynes or alkenes to provide 5,6-ring systems (e.g., **3a,b**) (Scheme 2). The Rh catalyst is proposed to insert into the C−C single bond of **1**, and following migratory insertion of CO, rhodacyclopentenones **2** are generated. These then combine with the tethered π-unsaturate to provide the product. For processes involving

Scheme 2. Rh-Catalyzed Carbonylative (3 + 1 + 2) Cycloadditions of Cyclopropenes with Alkynes and Alkenes



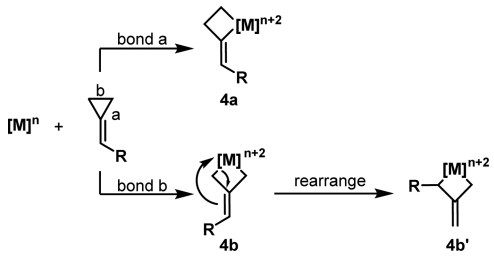
alkenes, high trans diastereoselectivity was observed for the newly formed ring junction.

Wang and co-workers[18] further exploited Rh insertion into cyclopropenes to effect rearrangement of systems possessing adjacent cyclopropylsilyl ethers, which provided cyclohexenones. Further developments in this area have been limited. However, although outside of the scope of this review, C−C cleavage of cyclopropenes has received significant recent attention as a means of accessing metallacarbenoids.[19] Other developments in the wider area of cyclopropene-based chemistry were reviewed in 2011.[20]

2.2. Alkylidenecyclopropane-based Processes

Alkylidenecyclopropanes (ACPs), although less strained than cyclopropenes (approximate strain energies of 39 vs 55 kcal/mol),[13] are still highly reactive to C−C oxidative addition.[15,21−23] Here, metal insertion can occur into proximal bond a or distal bond b, with examples of both types of process reported recently (Scheme 3). The resulting metallacyclobu-

Scheme 3. Transition-Metal Insertion into Alkylidenecyclopropanes



tanes (**4a/b**) are either captured directly or, for **4b**, allowed to rearrange prior to engagement with a tethered π-unsaturated component. Building on studies by Noyori et al.[24,25] in the 1970s with Ni catalysts, which tend to insert into bond a, cycloadditions catalyzed by a range of transition metals (Ni, Ru, Pd, and Rh) have emerged, and this area has been reviewed.[26,27]

For subsequent discussion, it is pertinent to summarize a 2003 report from Mascareñas and co-workers,[28] who developed palladium-catalyzed (3 + 2) cycloadditions of ACPs with pendant alkynes to generate bicyclic systems (e.g., **9a,b**) (Scheme 4). Computational studies support initial insertion of the palladium complex into the distal C−C bond of **5**, followed by isomerization (to **7**) and coordination to the tethered alkyne.[29] Carbometalation and reductive elimination then affords the products in good to excellent yields. Subsequent developments from the Mascareñas group included substantial

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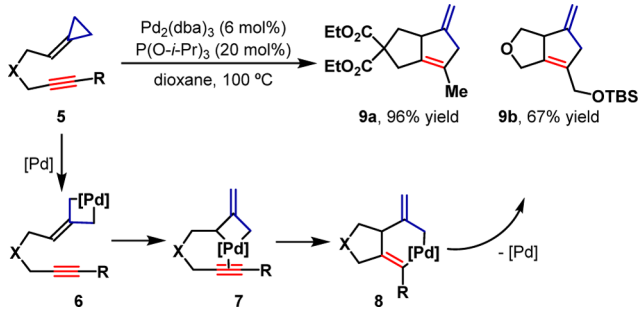
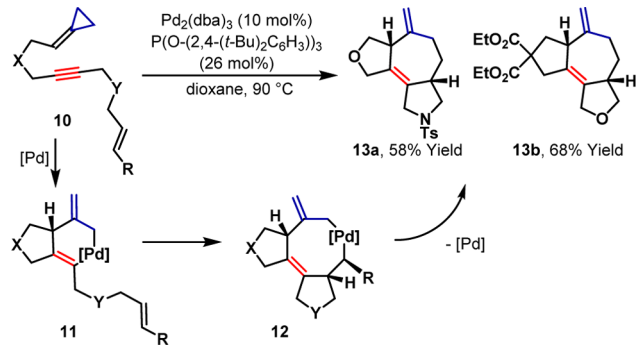
Scheme 4. Pd-Catalyzed Cyclizations of Alkylidenecyclopropanes with Tethered Alkynes



rate enhancements by use of bulkier phosphite ligands,[30] identification of complementary Ru-based systems,[31] and processes where the alkyne is replaced by an alkene.[32]

The process in Scheme 4 involves three distinct organometallic intermediates, each of which could serve as the basis for further reaction development. Indeed, trapping of **7** with other inserting groups was quickly realized to provide flexible access to other ring systems. For example, replacement of the alkyne with allenes generates [3.3.0] ring systems with an additional exocyclic methylene group.[33] Alternatively, use of 1,3-dienes provides direct access to challenging [5.3.0] ring systems.[34] Perhaps more interesting is the prospect of trapping palladacycle **8** prior to reductive elimination. In 2010, Mascareñas and co-workers[35] achieved this by including an additional tethered alkyne/alkene (Scheme 5). Here, formation

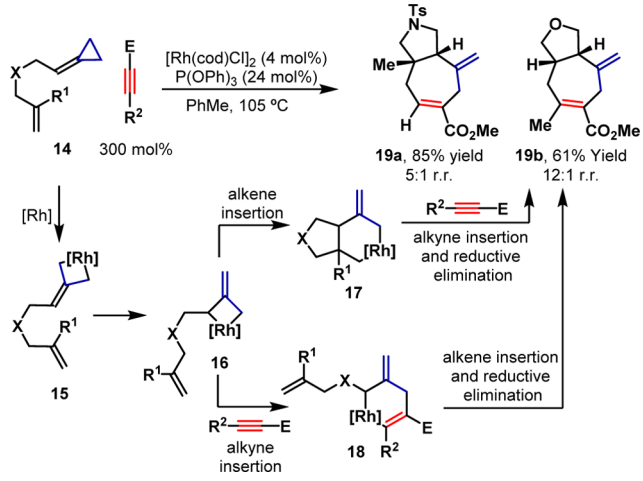
Scheme 5. Pd-Catalyzed (3 + 2 + 2) Cycloadditions of Alkylidenecyclopropanes



of palladacycle **11** is followed by insertion of the alkene (to **12**) or alkyne (not depicted) and reductive elimination of the (3 + 2 + 2) cycloaddition product. A key issue was suppression of competing reductive elimination from **11**, a process that still dominated in some cases under optimized conditions. It was reported in 2014[36] that a Rh-based catalyst system could completely address this issue, providing (3 + 2 + 2) adducts as the sole product as well as offering more general substrate scope. Computational studies suggested that, for Rh-based systems, reductive elimination from the (3 + 2) intermediate (cf. **11**) is significantly higher in energy than from the (3 + 2 + 2) intermediate (cf. **12**).[36,37]

The Rh-catalyzed (3 + 2 + 2) process of Mascareñas and co-workers[36] was predated by a report from Evans and Inglesby in 2008,[38] which disclosed powerful partially intermolecular (3 + 2 + 2) cycloadditions using alkylidenecyclopropanes (Scheme 6). Here, exposure of substrates **14** and electron-deficient alkynes

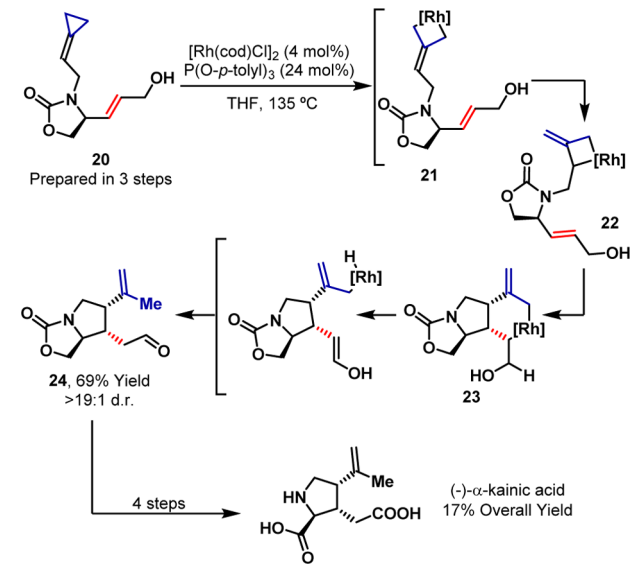
Scheme 6. Partially Intermolecular Rh-Catalyzed (3 + 2 + 2) Cycloadditions of Alkylidenecyclopropanes, Alkenes, and Polarized Alkynes



to a phosphite-ligated neutral Rh(I) system generated bicyclic products (e.g., **19a,b**) with regioisomeric ratios (rr) between 4:1 and >19:1. Two mechanistic pathways were proposed (vide infra), both involving initial insertion of the Rh(I) catalyst into the distal cyclopropane bond (cf. Scheme 4). Rearrangement to rhodacyclobutane **16** is followed by either alkene−alkyne or alkyne−alkene insertion and then reductive elimination to afford the product. The chemistry provides concise access to complex bicyclic systems and enabled a three-step synthesis of the cyclic sesquiterpene natural product pyrovellerolactone.[39] Subsequently, related processes using trialkoxysilyl-substituted alkenes were reported; these provided higher reaction rates and regioselectivities versus the process in Scheme 6.[40]

By omitting the alkyne component and using internal alkenes, related Rh-catalyzed ene-cycloisomerizations can be achieved.[41] The process is most aptly exemplified by its application to an elegant eight-step synthesis of (−)-α-kainic acid (Scheme 7). Here, exposure of serine-derived precursor **20** to a neutral Rh(I) system leads to rhodacyclobutane **22** via

Scheme 7. Rh-Catalyzed Ene-Cycloisomerization en Route to (−)-α-Kainic Acid



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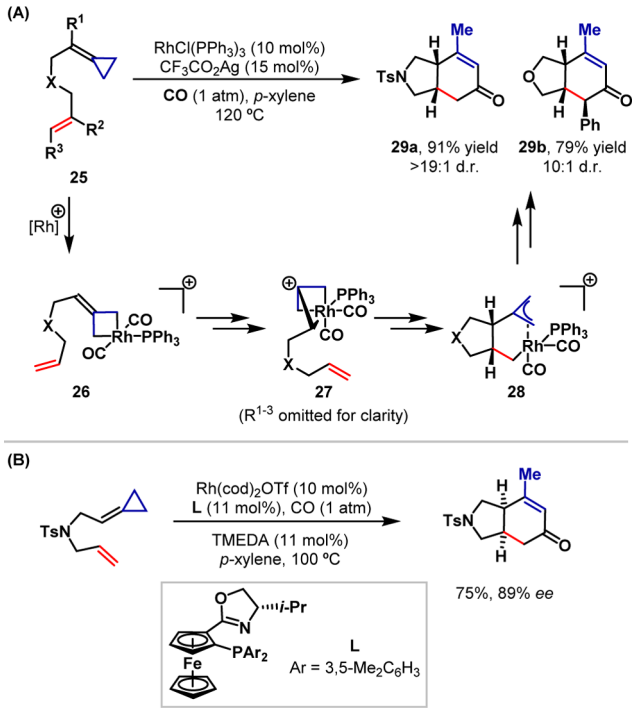
initial oxidative addition intermediate **21**. Insertion of the alkene is then followed by exocyclic β-hydride elimination (from **23**) and C−H reductive elimination to afford bicycle **24** in 69% yield and >19:1 diastereomeric ratio (dr). The proposed mechanism is supported by deuterium labeling studies on a related substrate.

More recent studies from Evans and co-workers[42] have focused on gaining an in-depth understanding of the isomerization process that occurs after oxidative addition of Rh(I) into alkylidenecyclopropanes. By use of a cationic Rh(I) system modified with PPh_3, generated in situ, substrates **25** engage in (3 + 1 + 2) cycloadditions with CO to generate cyclohexenones (e.g., **29a,b**) (Scheme 8A). Preliminary results with a chiral P,N

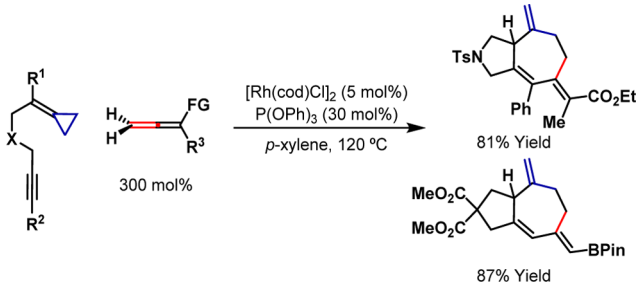
Scheme 8. Rh-Catalyzed Carbonylative (3 + 2 + 1) Cycloadditions and a Computationally Supported Mechanism



ligand system revealed promising levels of enantioselectivity (Scheme 8B). Computational studies support a scenario wherein isomerization of initial rhodacyclobutane **26** provides Rh(III) trimethylenemethane complex **27**. Alkene insertion then leads to η^3-allyl complex **28**. From here, migratory insertion of CO, C−C reductive elimination, and alkene isomerization affords the targets. Cyclizations of more highly substituted alkylidenecyclopropanes were also disclosed. Note that nickel analogues of **27** were previously ruled out as intermediates in alkylidenecyclopropane (3 + 2) cycloadditions (vide infra).[24,25] Later, Kim and Chung[43] reported a process related to that shown in Scheme 8A, where the alkene was replaced by an alkyne to generate phenols.

Subsequent studies succeeded in isolating and characterizing neutral rhodium complexes related to **27**; these underwent insertion of alkynes and CO and were also shown to be catalytically competent.[44] By employing these isolable metallacycles as a starting point, (3 + 2 + 2) cycloadditions involving exogenous allenes were demonstrated, and this led to a catalytic protocol (Scheme 9).[45] The approach enables the preparation

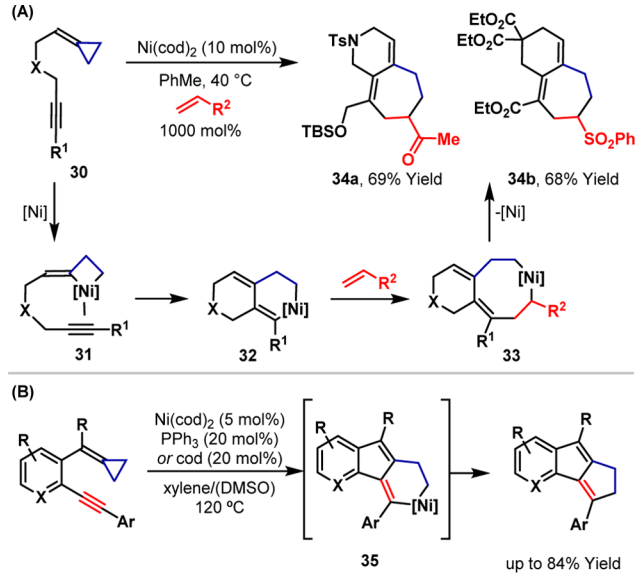
Scheme 9. Rh-Catalyzed (3 + 2 + 2) Cycloadditions of Alkylidenecyclopropanes, Alkynes, and Allenes



of challenging seven-membered rings bearing allene-derived tri- and tetrasubstituted exocyclic olefins; the geometry of this unit is controlled by preferential syn-carbometalation of the less hindered face of the terminal allene π-bond. It was also shown that the approach can be used for construction of 6,7-bicyclic systems by increasing the alkyne tether length.

Although ligand-dependent, it has been known since the 1970s that Ni-catalyzed cycloadditions of alkylidenecyclopropanes often proceed via direct insertion into the proximal C−C bond,[24,25] rather than into the distal C−C bond. This contrasts the Pd- and Rh-catalyzed processes discussed so far and enables access to different ring systems from the same precursors. Mascareñas and co-workers[46] exploited this observation to develop cycloadditions of precursors **30** that provided 6,7-bicyclic systems (e.g., **34a,b**) (Scheme 10A; cf. Scheme 6).

Scheme 10. (A) Ni-Catalyzed (3 + 2 + 2) Cycloadditions of Alkylidenecyclopropanes, Alkynes, and Alkenes and (B) Ni-Catalyzed (3 + 2) Cycloadditions of Alkylidenecyclopropanes and Alkynes



Here, insertion of Ni into the proximal C−C bond generates nickelacyclobutane **31**, which is converted to nickelacyclohexene **32** by insertion of the tethered alkyne. Compound **32** does not undergo reductive elimination and, instead, engages an exogenous alkene to generate the product via **33**. In certain cases, direct trapping of **31** by the alkene was observed to provide five-membered ring products. Computational studies were used to support the proposed mechanism, and these

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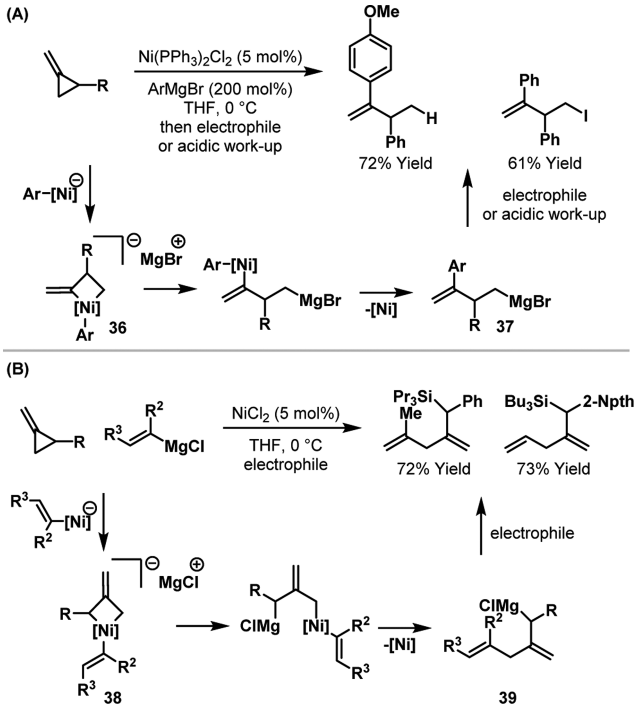
suggested that the alkyne directs Ni insertion. Subsequent studies demonstrated that nickelacycles related to **32** could be trapped by tethered alkynes or alkenes to provide complex tricyclic ring systems (cf. Scheme 5).[47] Additionally, Zhang and co-workers[48] adapted this initiation mode to provide benzofused ring systems, by promoting reductive elimination from nickelacyclohexene intermediates **35** (Scheme 10B).

In addition to the cycloaddition processes discussed so far, intermolecular couplings of methylenecyclopropanes have been developed. Kambe, Terao, and co-workers[49] showed that Ni-catalyzed multicomponent coupling of methylenecyclopropanes with aryl or vinyl Grignard reagents generates α-substituted styrenes (Scheme 11A) or skipped dienes (Scheme 11B). The

Scheme 11. Ni-Catalyzed Multicomponent Cross-Couplings of Methylenecyclopropanes

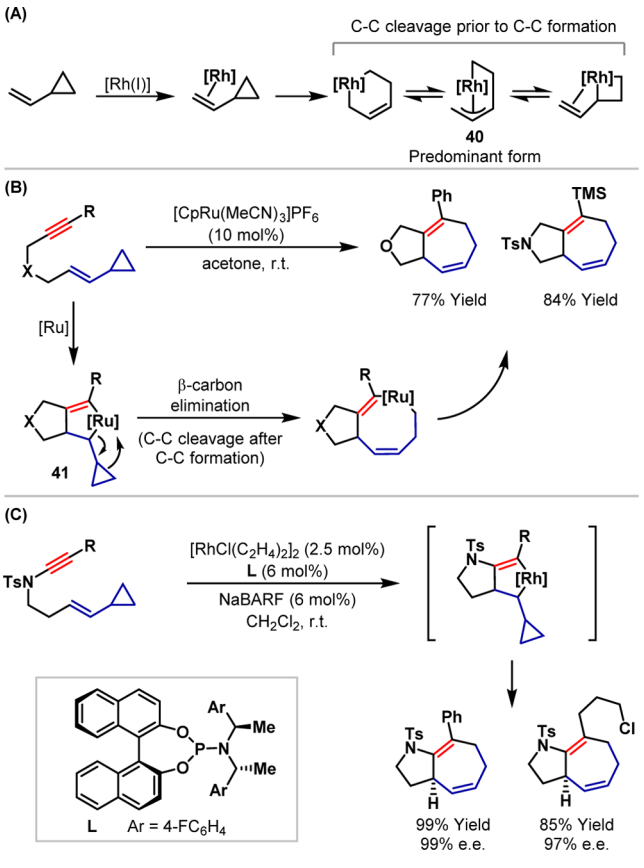


proposed mechanism for both processes involves generation in situ of an anionic organo-Ni(0) species that inserts into either the proximal or distal methylenecyclopropane C−C bond to generate nickelacycle **36** or **38**. These undergo ring opening and C−C reductive elimination to release new Grignard reagents **37** and **39**, which are quenched either on workup or in situ (alkyl halides/R_3SiCl). The proposed mechanisms were supported by deuterium labeling studies.

2.3. Vinylcyclopropane-based Processes

The three-membered ring systems discussed so far possess very high levels of ring strain, due to the adjacent or fused π-unsaturation. Cyclopropanes embody significantly lower strain energy than cyclopropenes or alkylidenecyclopropanes,[13] rendering them more challenging substrates for C−C activation. However, following the seminal studies of Wender et al.,[50] where, under Rh-catalyzed conditions, vinylcyclopropanes (VCPs) were established as five-carbon units for (5 + 2) cycloaddition reactions,[51,52] catalysis based on this activation mode has received significant attention. In general, the mechanism of these processes involves initial π-coordination of Rh to the vinylcyclopropane, which triggers C−C bond cleavage to provide π-allyl rhodacycles **40** (Scheme 12A). In the resulting cycloadditions, either all five carbons of the vinyl-

Scheme 12. (A) Oxidative Addition of Rh(I) Catalysts to Vinylcyclopropanes and Mechanistically Distinct (B) Ruthenium- and (C) Rhodium-Catalyzed Processes



cyclopropane unit or the three carbons of the cyclopropane are transferred to the new ring. Several reviews deal with this topic, as well as other transition-metal-catalyzed processes involving vinylcyclopropanes.[9,51−54] Note that related Ru-catalyzed (5 + 2) processes reported by Trost and co-workers[55,56] likely proceed via a distinct mechanism involving oxidative coupling (to **41**) in advance of β-carbon elimination and C−C reductive elimination (Scheme 12B). Interestingly, computational studies support a similar scenario for enantioselective Rh-catalyzed intramolecular (5 + 2) cycloadditions of ynamides and VCPs developed recently by Anderson and co-workers (Scheme 12C);[57] in this study, elegant catalyst-controlled diastereoselective processes were also outlined.

The Wender laboratory has extended the range of processes where vinylcyclopropanes are used as five-carbon components in cycloadditions. Alkoxy-substituted vinylcyclopropanes such as **42** are especially effective in intermolecular processes. Indeed, previous studies demonstrated that **42** participates in carbonylative (5 + 2 + 1) and (5 + 1 + 2 + 1) cycloadditions with alkynes[58,59] and (5 + 2 + 1) or (5 + 2) cycloadditions with allenes;[60] the latter process has been the subject of a computational study.[61] More recently, it was shown that Rh-catalyzed cycloaddition of **42** with enynone **43** generates seven-membered ring **44** in an efficient manner (Scheme 13A).[62] Note that the cyclic ketone is released by hydrolysis of an initially formed enol ether. Nazarov cyclization of **44** then

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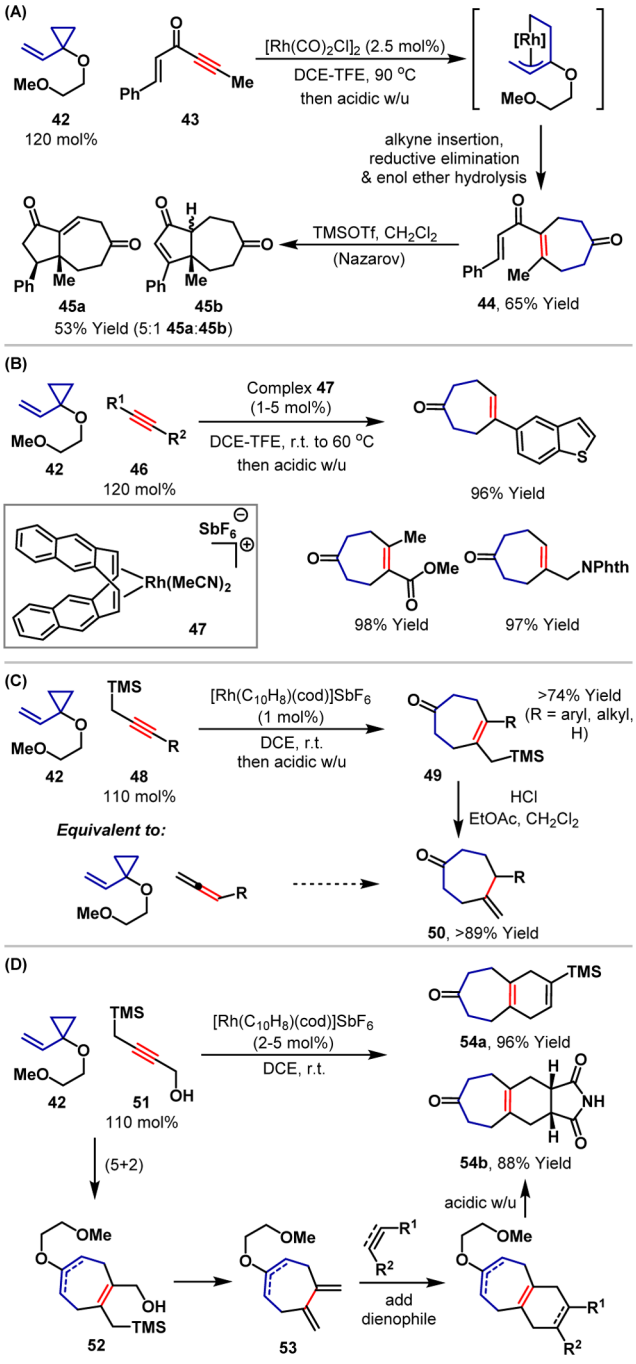
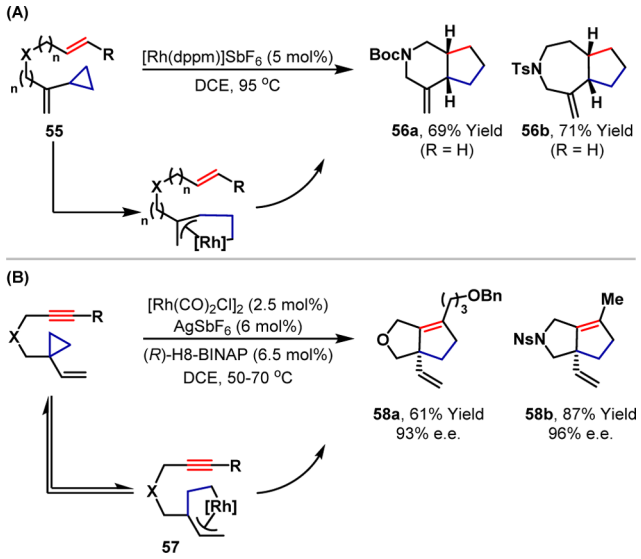
Scheme 13. Intermolecular (5 + 2) Cycloadditions of Vinylcyclopropanes with Alkynes



provides bicyclic systems **45a** and **45b** in 5:1 selectivity. The two-step sequence was demonstrated with a wide range of enynones and provides a powerful entry to complex bicyclic systems. The mechanism of (5 + 2) cycloadditions of vinylcyclopropanes with simpler alkynes has been probed computationally, and this has provided a rationale for the regioselectivity of alkyne insertion.[63] Subsequent studies showed that cationic Rh systems can promote (5 + 2) cycloadditions of **42** with alkynes at room temperature.[64,65] This led to the development of complex **47**, which is a highly efficient catalyst for a variety of vinylcyclopropane-based cycloadditions, including (5 + 2) variants (Scheme 13B).[66,67] Under cationic Rh-catalyzed conditions, propargyltrimethylsilanes function as allene equivalents in (5 + 2) cycloadditions with vinylcyclopropanes (Scheme 13C).[68] Here, initial cycloaddition generates **49**, which is then subject to acid-promoted protodesilylation to provide exocyclic alkene products **50**; a one-pot process was also reported. This concept was extended to processes involving (5 + 2) cycloaddition of alcohol **51**, which provides intermediate **52** (Scheme 13D).[69] Facile elimination of the TMS and OH groups from **52** (perhaps by a vinylogous Peterson elimination) generates diene **53**, which undergoes Rh-catalyzed or thermal (4 + 2) cycloaddition with a variety of dienophiles to provide fused ring systems, such as **54a,b**.

The Yu group has focused recently on the use of vinylcyclopropanes as three-carbon units in cycloaddition reactions. For example, systems **55** undergo Rh-catalyzed carbonylative (3 + 2) cycloaddition to provide a range of bicyclic systems (e.g., **56a,b**), where the vinyl moiety of the VCP is incorporated as an *exo*-methylene substituent (Scheme 14A).[70] In these processes, potential (5 + 2) cycloaddition

Scheme 14. Intramolecular (3 + 2) Cycloadditions of Vinylcyclopropanes with Alkenes or Alkynes



products were not observed, and systems where R ≠ H reacted less efficiently. Replacement of the alkene unit with an alkyne led to fused bicyclic cyclopropane products (not depicted). By switching the position of attachment of the tethered π-unsaturate, other ring systems can be generated. For example, (3 + 2) cycloaddition with alkynes delivered [3.3.0] ring systems (e.g., **58a,b**) in high yield and enantiomeric excess (ee) by use of a cationic Rh system modified with (*R*)-(+)-2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl [(*R*)-H8-BINAP] (Scheme 14B).[71] Computational studies support reversible rhodacycle (**57**) formation in advance of stereodetermining alkyne insertion. Related (non-enantioselective) processes involving alkenes and allenes were also reported.[72]

The Yu laboratory has also reported higher-order carbonylative cycloadditions using similar substrates: (3 + 2 + 1) cycloadditions of substrates **59**, which involve tethered alkenes or alkynes, provided new fused cyclohexanone (e.g., **60a**) or cyclohexenone (e.g., **60b**) ring systems (Scheme 15A).[73] Presumably carbonylation occurs after the π-unsaturate has

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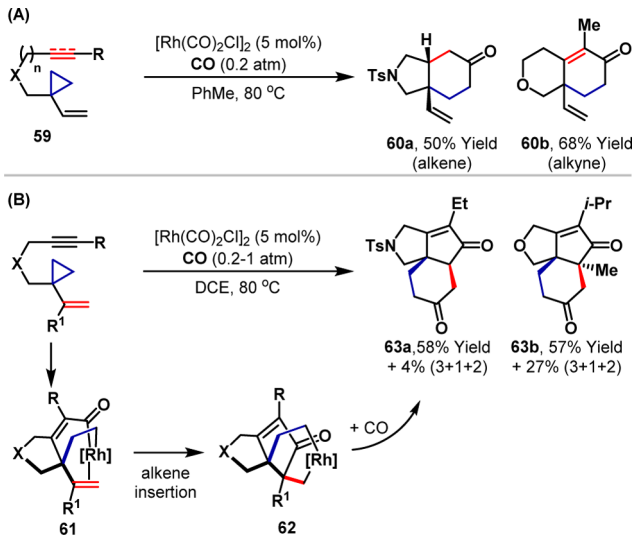
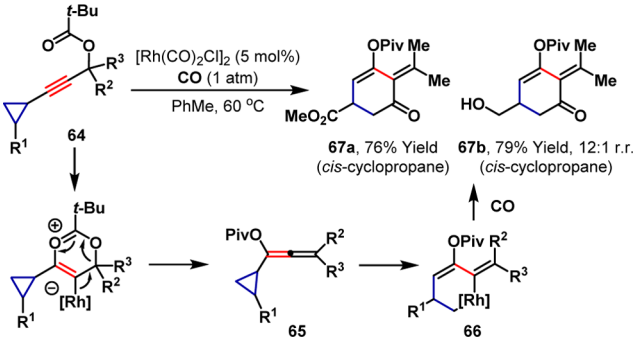
Scheme 15. Higher-Order Carbonylative Cycloadditions of Vinylcyclopropanes



inserted in the initially generated rhodacycle. Indeed, subsequent studies involving internal alkynes provide angularly fused tricyclic ring systems (e.g., **63a,b**) (Scheme 15B).[74] In essence, these processes represent interrupted variants of those outlined in Scheme 15A. Thus, rather than C−C reductive elimination at the stage of **61**, alkene migratory insertion occurs to provide new rhodacycle **62**, which then undergoes carbonylation and C−C reductive elimination to generate the products. During optimization, a product derived from C−C reductive elimination of **62** was observed, albeit in small quantities. Yu and co-workers have also developed carbonylative (5 + 1) cycloadditions to prepare cyclohexenones[75] and a carbonylative (5 + 2 + 1) cycloaddition−aldol cascade to prepare hirsutic acid.[76]

Cyclopropanes with other classes of adjacent C-based π-unsaturation are also active in Rh-catalyzed cycloadditions. An interesting example was reported by Tang and co-workers in 2011,[77] involving generation of allenylcyclopropanes in situ (Scheme 16). Here, Rh-catalyzed rearrangement of propargylic pivalates **64** (and acetates) leads to allenyl intermediates **65**. Oxidative addition of the Rh catalyst is followed by carbonylation of rhodacycle **66** and C−C reductive elimination to generate complex cyclohexenone ring systems (e.g., **67a,b**). The method is effective with both *cis*- and *trans*-cyclopropanes as well as more heavily substituted variants. For the processes in

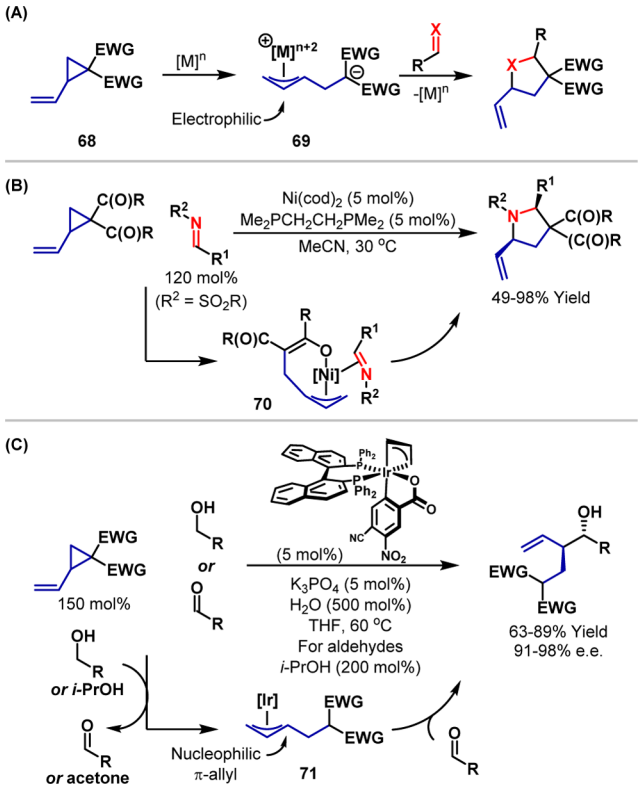
Scheme 16. In Situ Generation and Carbonylation of Allenyl Cyclopropanes



Scheme 16, preferential cleavage of the less hindered cyclopropane C−C bond accounts for the observed regioselectivities. Rh-catalyzed rearrangement of allenyl vinylcyclopropanes, generated in situ by the same method, led to seven-membered carbocycles.[78] Similar ring systems have been generated by use of preformed allenylcyclopropanes, and this provided a formal synthesis of (−)-galanthamine.[79]

Another key area of catalysis based on oxidative addition of transition metals to vinylcyclopropanes involves donor−acceptor systems **68**, which are set up for S_N2-like oxidative addition (Scheme 17A). This generates simultaneously an electrophilic

Scheme 17. Metal-Catalyzed Cycloaddition and C−C Bond Formation by Use of Donor−Acceptor Vinylcyclopropanes[a]



[a]EWG = electron-withdrawing group.

π-allyl and a stabilized carbanion (**69**), thus rendering this activation mode suitable for formal cycloaddition processes involving polarized π-unsaturates. Recent contributions include Pd-catalyzed enantioselective cycloadditions with polarized alkenes, as reported by Trost and Morris,[80,81] and Fe-catalyzed homoconjugate additions of Grignard reagents, as reported by Sherry and Fürstner.[82] Plietker and co-workers[83] subsequently demonstrated Fe-catalyzed cycloadditions involving electron-deficient alkenes. Matsubara and co-workers[84] developed Ni-catalyzed cycloadditions with imines to provide vinylpyrrolidines (Scheme 17B). This process is distinct from the outline given in Scheme 17A, as it is proposed to proceed via a nickelacyclic intermediate (**70**) rather than a metal π-allyl (**69**). Preliminary studies suggest that highly enantioselective variants should be feasible. Earlier, Kimura and co-workers[85] developed Ni-catalyzed reductive couplings with alkynes to provide skipped dienes based on the same activation mode. Johnson, Krische, and co-workers[86] reported polarity inversion of donor−acceptor cyclopropanes under Ir-catalyzed transfer

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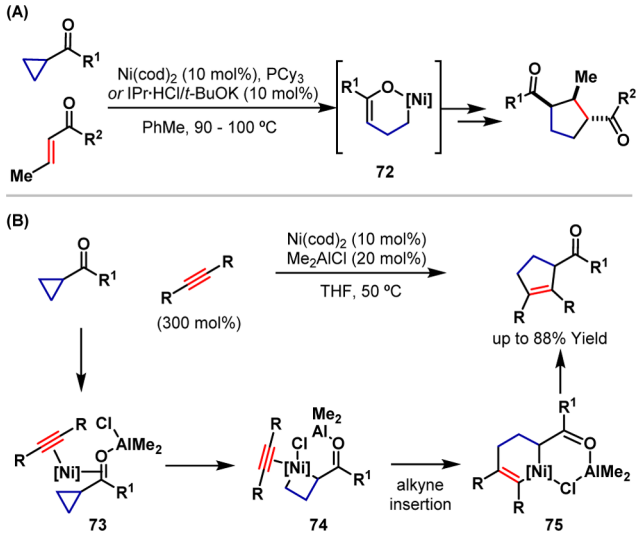
hydrogenative conditions (Scheme 17C). The process converts the vinylcyclopropane precursor into a neutral nucleophilic metal allyl (**71**), which can engage with aldehydes (generated in situ) to provide homoallylic alcohols with high diastereo- and enantioselectivity. The reductant for the process is provided either by dehydrogenation of an alcohol coupling partner, which generates the aldehyde electrophile in situ, or by exogenous isopropyl alcohol (for aldehyde starting materials). This area of catalysis has been reviewed recently.[87] Later, Mita et al.[88] reported the generation of nucleophilic Pd-allyls by use of $ZnEt_2$ as reductant and showed that these react smoothly with carbon dioxide.

2.4. Cyclopropyl Ketone- and Imine-based Processes

The examples discussed so far highlight recent progress in the development of processes involving C−C cleavage of cyclopropanes possessing fused or adjacent C-based π-unsaturation (i.e., vinylcyclopropanes and alkylidenecyclopropanes). However, recent years have also seen significant interest in C−C cleavage methodologies that use cyclopropanes activated by adjacent electron-withdrawing π-unsaturation (e.g., ketones). Such processes are inherently appealing because of the easy accessibility of the substrates, including highly substituted and/or enantiopure precursors. Liu and Montgomery[89,91] and Ogoshi and co-workers[90,92,93] have demonstrated that cyclopropyl ketones or imines can engage alkenes to provide cyclopentanes in the presence of Ni catalysts. For cyclopropyl ketone-based processes, six-membered ring oxanickelacycles **72** were identified as key intermediates (Scheme 18A).[92,93]

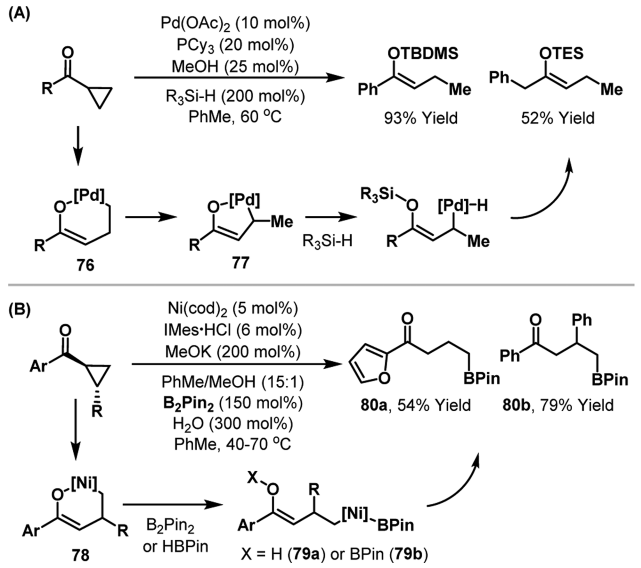
Scheme 18. Nickel-Catalyzed (3 + 2) Cycloadditions of Cyclopropyl Ketones with (A) Alkenes and (B) Alkynes



However, replacement of the alkene with alkyne did not facilitate related cyclopentene formations. Ogoshi and co-workers[93] have addressed this issue by developing a method that employs Me_2AlCl as a Lewis acidic additive (Scheme 18B). In the proposed mechanism, Me_2AlCl activates the ketone and facilitates coordination of an alkyne-ligated Ni(0) complex (**73**). C−C oxidative addition provides nickelacyclobutane **74**, which is stabilized by coordination to the chloride ligand of the ligated Lewis acid. Subsequent insertion of the alkyne is followed by reductive elimination of the (3 + 2) cycloaddition product from **75**. Stoichiometric experiments suggest that nickelacyclobutane **74** *does not isomerize* to an oxanickelacyclohexene (cf. **72**), presumably because of stabilization of the four-membered ring by the bridging chloride ligand. Processes involving unsymmetrical alkynes often proceeded with good levels of regioselectivity.

The Oshima group has also developed metal-catalyzed hydrometalations of cyclopropyl ketones. Under Pd-catalyzed conditions, various trialkylsilanes combine with cyclopropyl ketones to provide silyl enol ethers with high (*Z*)-selectivity (Scheme 19A).[94] The proposed mechanism invokes oxidative

Scheme 19. (A) Pd-Catalyzed Hydrosilylation and (B) Ni-Catalyzed Formal Hydroborylation of Cyclopropyl Ketones



addition by a Pd(0) complex, generated in situ, to provide palladacycle **76**. This isomerizes to five-membered palladacycle **77** by a β-hydride elimination−hydrometalation sequence. Transmetalation with the silane is followed by C−H reductive elimination to deliver the product. The proposed mechanism is supported by deuterium labeling studies. Ni(0) systems will also insert into aryl cyclopropyl ketones to provide nickelacycles **78** (Scheme 19B).[95] Possible subsequent mechanistic pathways involve capture by B_2Pin_2 to provide either enol ethers **79a** or boron enolates **79b**, which, upon workup, provide γ-borylated ketones (e.g., **80a,b**). The process was also demonstrated on 1,1-disubstituted cyclopropanes.

Other metals have been shown to insert into specific subclasses of cyclopropyl ketone. Zhang et al.[96] effected carbonylative isomerization of alkynyl systems **81** to bicyclic furans (e.g., **84a,b**) (Scheme 20). The proposed mechanism involves C−C oxidative addition prior to rearrangement of **82** to five-membered rhodacycle **83**. Insertion of CO and reductive elimination then provide the products.

2.5. Processes Based on Less Activated Cyclopropanes

Metal-catalyzed activation of nonactivated cyclopropanes is well-established but rarely used in catalysis outside of reduction and simple isomerization processes.[9,97] Application of this activation mode to more productive processes must address the key issues of metallacyclobutane stability and C−C oxidative addition regioselectivity; this latter issue arises because nonactivated cyclopropanes possess three electronically similar C−C bonds (Scheme 21).

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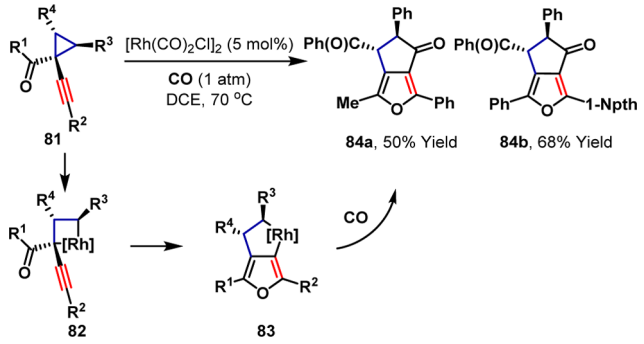
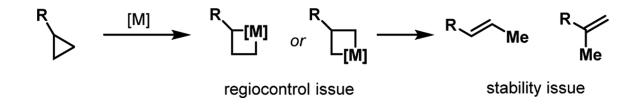
Scheme 20. Carbonylative Rearrangement of Alkynyl Cyclopropyl Ketones



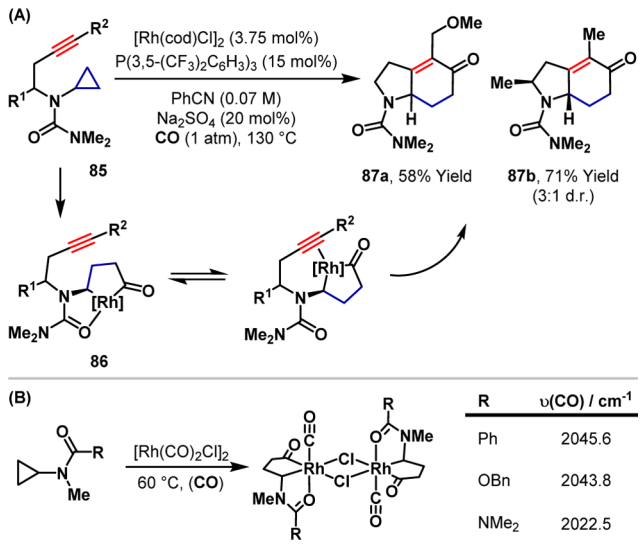
Scheme 21. Metal-Catalyzed Activation of Nonactivated Cyclopropanes



The stability issue can be addressed by fast capture of the incipient metallacyclobutane with CO to afford a metallacyclopentanone. Indeed, in 1968, Wilkinson and co-workers[98] demonstrated that carbonylative insertion of $[Rh(CO)_2Cl]_2$ into cyclopropane yields isolable rhodacyclopentanones. Subsequently, Koga and Narasaka[99] demonstrated Rh-catalyzed carbonylative (3 + 1 + 2) cycloadditions between cyclopropanes and tethered alkynes that proceed via a rhodacyclopentanone intermediate. In this process, regiocontrol was achieved by using the alkyne to direct C−C bond activation.

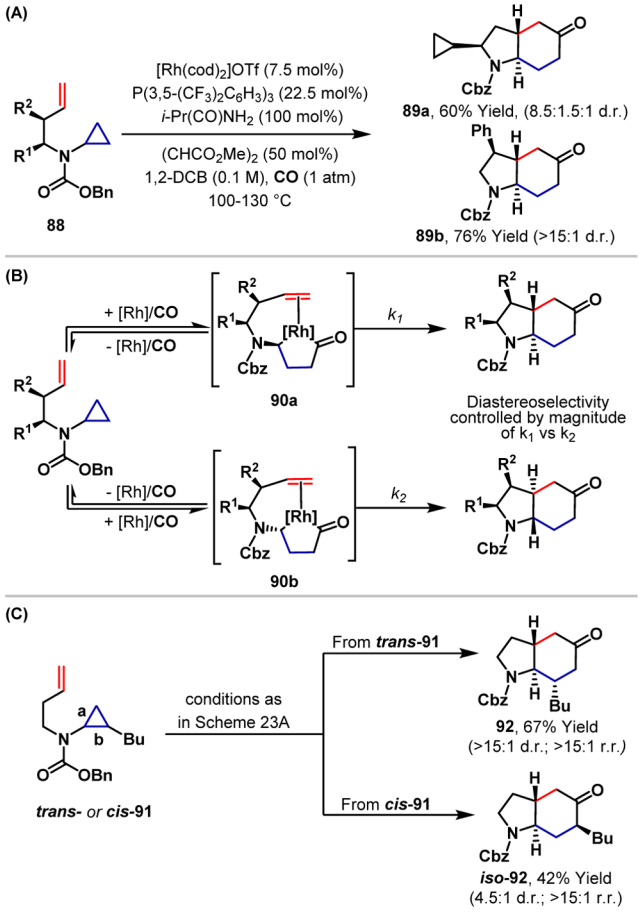
There have been significant recent developments in the area of rhodacyclopentanone-based catalysis,[100] which are discussed next. In 2013, Bower and co-workers[101] reported N-protecting-group-directed generation of rhodacyclopentanones as the basis for a (3 + 1 + 2) cycloaddition strategy (Scheme 22A). Here, systems **85**, equipped with urea directing groups, direct Rh/CO insertion into the proximal aminocyclopropane bond to generate selectively rhodacyclopentanones **86** (at the expense of two other regioisomeric possibilities). Dissociation of the directing group is followed by alkyne insertion and C−C reductive elimination to provide heterobicyclic enones (e.g., **87a,b**) in moderate to good yield. A second-generation cationic Rh(I) system provided faster reaction rates and higher yields for challenging susbtrates.[102] The activation mode was confirmed by the synthesis and characterization of model metallacyclic complexes (Scheme 22B). Analysis of the CO stretching frequencies of a range of analogues provided a quantitative measure of directing group strength.[103]

Scheme 22. Protecting-Group-Directed Carbonylative (3 + 1 + 2) Cycloadditions of Aminocyclopropanes and Alkynes



The process in Scheme 22A requires a strongly coordinating urea directing group to facilitate oxidative addition because of competitive binding of Rh(I) to the alkyne moiety of **85**.[101] Indeed, related cycloadditions involving less strongly coordinating alkenes proceed smoothly with weaker carbamate directing groups (e.g., carboxybenzyl, Cbz; Scheme 23A).[103]

Scheme 23. Protecting-Group-Directed Carbonylative (3 + 1 + 2) Cycloadditions of Aminocyclopropanes and Alkenes



Optimized conditions use a cationic Rh(I) system in combination with a stabilizing additive [*i*-Pr(CO)NH_2]. The C−C activation step is highly selective such that the cyclopropyl substituent of **89a** survives the reaction conditions. The high diastereoselectivities observed for R^1/R^2 substituted centers likely arise via reversible formation of diastereomeric rhodacyclopentanones **90a** and **90b** in advance of diastereodetermining alkene insertion (Scheme 23B). Exchange studies, involving stoichiometrically generated rhodacyclopentanones, support this supposition. Retrocarbonylation from **90a,b** requires a vacant coordination site on the Rh center. As

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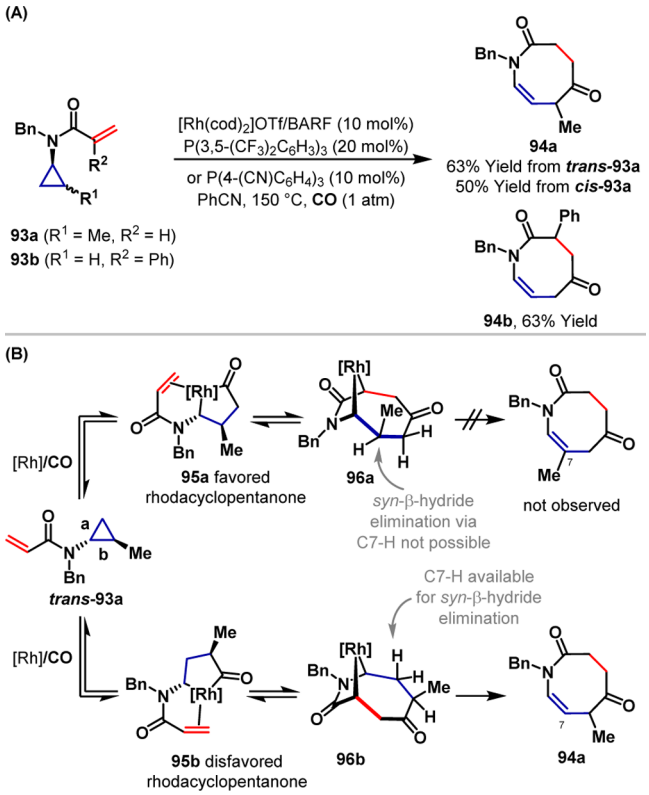
such, the use of more coordinatively saturated neutral Rh(I) systems for the cycloadditions in Scheme 23A led to low diastereoselectivity. Processes involving disubstituted cyclopropanes were developed and revealed interesting regioselectivities for cycloaddition (Scheme 23C). Trans-disubstituted systems (e.g., *trans*-**91**) underwent preferential activation at the less hindered bond a to deliver adduct **92**, wherein the relative stereochemistry of the cyclopropane starting material is transferred to the product. Conversely, activation of cis-disubstituted system *cis*-**91** occurred at the more hindered bond b to provide regioisomeric adduct *iso*-**92**.

Bower and co-workers[104] extended their approach to carbonylative cycloadditions of *N*-cyclopropylacrylamides **93** (Scheme 24A). This delivered highly strained (7 + 1) cycloadducts (e.g., **94a,b**) in moderate to excellent yield. An interesting observation was that both *cis*- and *trans*-cyclopropane substrates (e.g., *cis*/*trans*-**93a**) delivered the same regioisomer of the product (**94a**), derived from activation of the more hindered bond b (Scheme 24B; cf. Scheme 23C). This was rationalized by invoking both reversible rhodacyclopentanone formation and reversible alkene insertion. Alkene insertion into favored rhodacyclopentanone **95a** delivers metallacycle **96a**, wherein syn-β-hydride elimination via C7−H is not possible. However, equilibration via disfavored rhodacyclopentanone **95b** provides regioisomeric metallacycle **96b**, which is set up for syn-β-hydride elimination and C−H reductive elimination to provide the observed regioisomer. Note that β-hydride elimination via C4−H is disfavored, likely due to the high strain of accommodating five adjacent sp^2 centers within the eight-membered ring that would result.

Scheme 24. Protecting-Group-Directed Carbonylative (7 + 1) Cycloadditions of Aminocyclopropanes and Alkenes

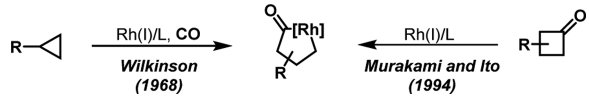


The processes outlined above represent the major developments in this area, although there have been other sporadic reports of C−C activation involving relatively nonactivated cyclopropanes. For example, René et al.[105] have shown that Pd(0) systems will insert into spirocyclopropanes to allow ring expansion to caprolactams and azepanes.

2.6. Cyclobutanone- and Benzocyclobutenone-based Processes

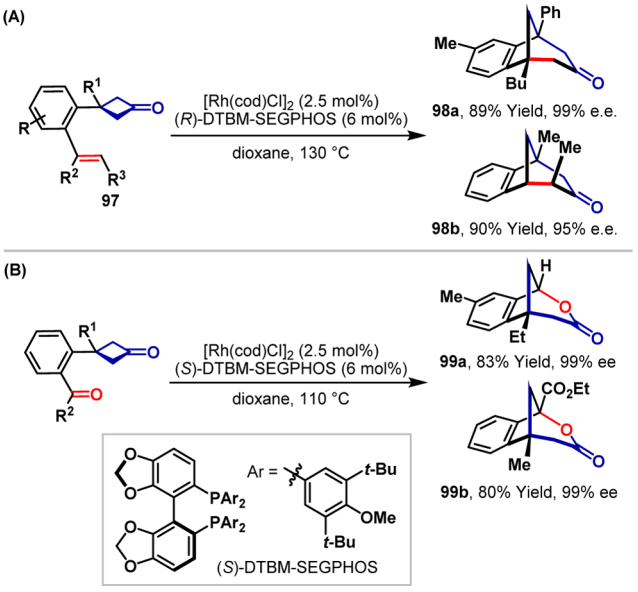
Seminal studies by Murakami et al.[106] demonstrated non-directed insertion of Rh(I) catalysts into the C−C bond of ketones, including cyclobutanones. Subsequently, catalytic processes involving cyclobutanones were developed, with the approach providing an alternative entry to rhodacyclopentanones versus cyclopropane rhodacarbonylation (Scheme 25).[107] Recent years have seen significant development of this activation mode, with key methodologies outlined below; a comprehensive review covering catalysis based on rhodacyclopentanones has appeared recently.[100]

Scheme 25. Rhodacyclopentanones via C−C Bond Activation



Building upon earlier studies by Murakami et al.,[108] Cramer and co-workers[109,110] succeeded in rendering cyclobutanone π-insertion processes enantioselective (Scheme 26A). Here, styrenyl systems **97** underwent enantioselective C−C bond activation by use of a Rh(I) system modified with (−)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (DTBM-SEGPHOS). The resulting rhodacyclopentanone was captured by the alkene to provide complex bridged systems (e.g., **98a,b**) in high enantioselectivity. Other classes of π-unsaturates can also be exploited. Indeed, Souillart and Cramer[111] later showed that insertion of carbonyls provides lactones (e.g., **99a,b**) in high enantioselectivity

Scheme 26. Enantioselective π-Insertion into Cyclobutanones



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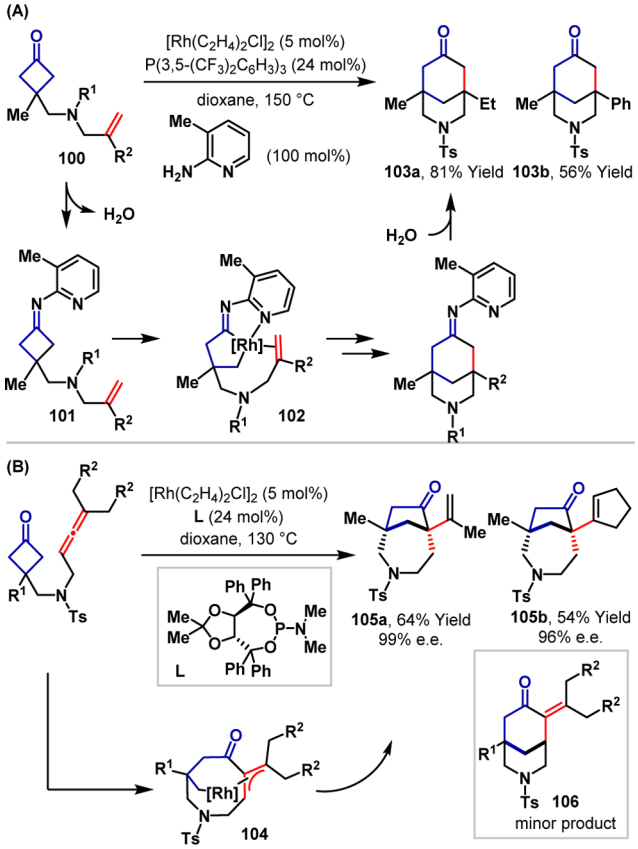
(Scheme 26B). Interestingly, the process tolerates aldehydes, even though these are prone to decarbonylation under Rh-catalyzed conditions.

Decarbonylation at the stage of the rhodacyclopentanone is often a major inefficiency associated with the cyclobutanone activation processes outlined here. To address this, Ko and Dong[112] adapted the pyridyl-directed C−C activation strategy of Jun and Lee[113] to cyclobutanone π-insertion processes (Scheme 27A). Exposure of cyclobutanones **100** to 2-amino-3-

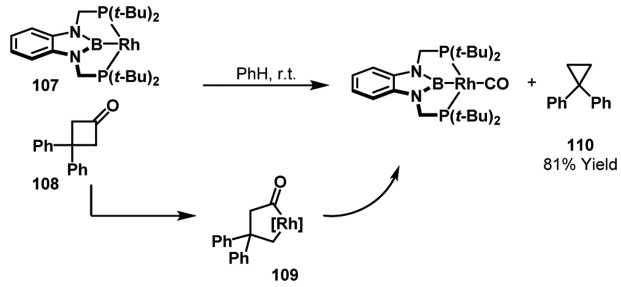
Scheme 27. (A) Temporary-Directing-Group-Assisted π-Insertion and (B) Nondirected Allene Insertion into Cyclobutanones



methylpyridine effected smooth conversion to imines **101**. These then direct C−C insertion of the rhodium catalyst to provide rhodacycles **102**. Insertion of the alkene is followed by C−C reductive elimination and imine hydrolysis to provide complex bridged heterocycles. Note that intermediate **102** cannot undergo decarbonylation (cf. **90a,b**). Examples involving 1,2-disubstituted alkenes were also disclosed. Subsequently, processes involving the insertion of allenes were developed; these did not require the pyridyl-assisted approach (Scheme 27B).[114] Rather than direct insertion of the allene to provide expected six-membered ring product **106**, isomerization was observed, likely via Rh-allyl **104**, to provide [4.2.1] bicycles (e.g., **105a,b**). In this process the allene acts as a formal carbene equivalent, providing a one-carbon unit to the newly formed cyclopentanone.

A significant issue is the high reaction temperatures required for C−C activation of cyclobutanones under Rh-catalyzed conditions. Recently, Murakami and co-workers[115] have demonstrated room-temperature activation of cyclobutanones (and benzocyclobutenones), using PBP pincer complex **107** (Scheme 28). This inserted smoothly into cyclobutanone **108**

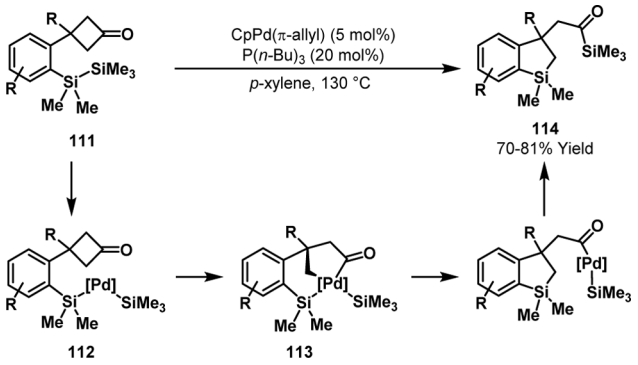
Scheme 28. Room-Temperature C−C Activation of a Cyclobutanone



to generate rhodacyclopentanone **109**, which underwent decarbonylation and C−C reductive elimination to release cyclopropane **110**. These studies indicate that the design of appropriate catalysts will ultimately allow milder C−C activation methodologies.

Complexes based on Rh are by far the most common for C−C activation of cyclobutanones. However, in directed settings, other metals might also be effective. Murakami and co-workers[116] have shown that activation of cyclobutanones **111** is possible under conditions of Pd catalysis (Scheme 29). In the

Scheme 29. Pd-Catalyzed Cyclobutanone C−C Bond Activation by Initial Insertion into a Proximal Si−Si Bond



proposed mechanism, initial Si−Si oxidative addition generates Pd(II) intermediate **112**, which triggers C−C activation to provide Pd(IV) complex **113**. Sequential C−Si reductive eliminations release the catalyst and provide products **114**, completing a formal σ-bond metathesis from **111**.

In 1992, Liebeskind and co-workers[117] showed that Wilkinson's catalyst can insert into the C(sp^3)−acyl bond of benzocyclobutenone to provide rhodaindanone **115a** (Scheme 30A). This underwent thermal isomerization to thermodynamically favored regioisomer **115b**. Recent computational studies suggest that this occurs via retrocarbonylation−recarbonylation from **115a**.[118] The Dong laboratory has exploited this activation mode to provide a wide range of methodologies. In the simplest manifestation, exposure of benzocyclobutenones **116** to phosphine-ligated Rh(I) systems was shown to effect rearrangement to benzocyclopentenones (e.g., **119a,b**) (Scheme 30B).[119] The mechanism likely involves a sequence of β-hydride elimination from rhodaindanone **117**, hydrometalation, and C−C reductive elimination from **118**. Other processes require rearrangement of the initially formed

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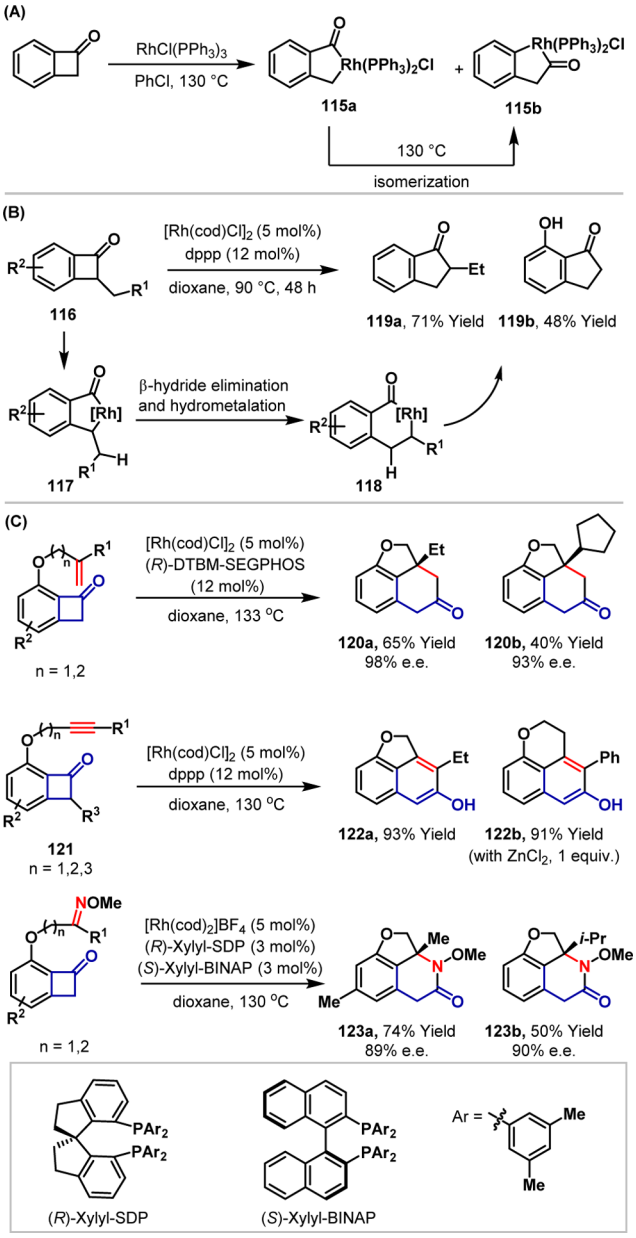
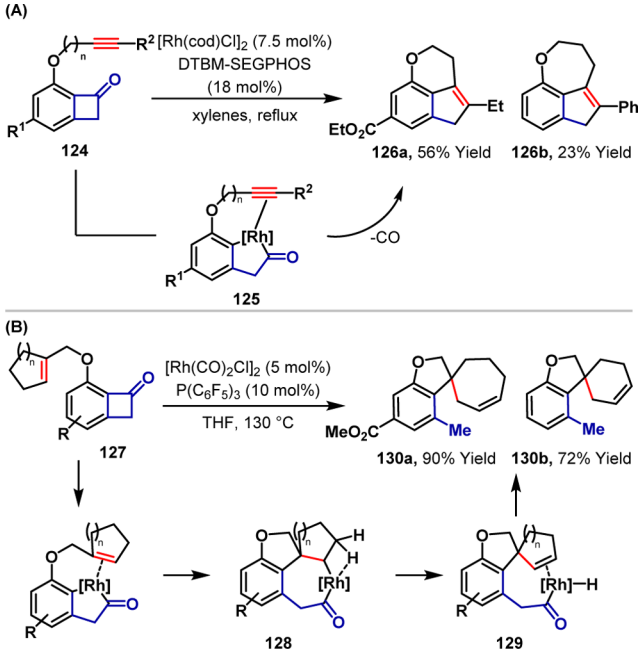
Scheme 30. Rhodaindanones and Associated Catalytic Processes



rhodaindanone to engage a tethered π-unsaturate (Scheme 30C; cf. Scheme 30A). For example, Rh-catalyzed insertion of tethered 1,1-disubstituted alkenes provides stereochemically complex tricycles (e.g., **120a,b**) with high enantioselectivity.[120,121] The process was extended to trisubstituted alkenes and applied to a short synthesis of cycloinumakiol.[122] Related processes involving alkynes **121** provide β-naphthol products (e.g., **122a,b**).[123] Heteroatom-based inserting groups have also been employed, with insertion of oximes generating complex lactam products (e.g., **123a,b**) with high enantioselectivity.[124] Here, a double chiral ligand system was employed, with (*R*)-(+)-7,7′-bis[di(3,5-dimethylphenyl)phosphino]-1,1′-spirobiindane [(*R*)-xylyl-SDP] providing higher selectivity and (*S*)-xylyl-BINAP providing higher turnover numbers, such that a combination of both was found to be optimal.

The Dong group has also found that related decarbonylative processes can be achieved. For example, when DTBM-SEGPHOS is used as ligand, cyclization of substrates **124** provides six- and seven-membered ring cyclic ethers (e.g., **126a,b**) fused to an indene ring (Scheme 31A).[123] CO loss

Scheme 31. Decarbonylative Cycloadditions of Benzocyclobutenones



possibly occurs at the stage of rhodaindanone **125**. Decarbonylative processes involving tethered alkenes (**127**) provide spirocyclic systems (e.g., **130a,b**) (Scheme 31B).[125] Computational studies indicate that the process proceeds via β-hydride elimination from alkene insertion intermediate **128**. This provides acyl-Rh hydride **129**, which undergoes decarbonylation and C−H reductive elimination to provide the products.[126]

The preceding discussion summarizes the major recent developments in C−C activation of four-membered rings, with cyclobutanone-based systems underpinning all the methodologies. Thus, internal activation of the cyclobutane ring is required, even though cyclobutane itself embodies only marginally less strain than cyclopropane (approximate strain energies of 26 vs 29 kcal/mol). Such a situation is likely reflective of differential orbital availability for bonding to transition metals. There has been limited progress in the development of other cyclobutane-based C−C activation methodologies, although recent reports from Matsuda et al.[127,128] concerning directed activation of (2-pyridylmethylene)cyclobutenes are of note. Further background on metal-catalyzed C−C cleavage of cyclobutane-based systems is available in a comprehensive review published in 2011.[129]

2.7. Biphenylene-based Processes

Due to its very high strain energy, biphenylene has the richest history in C−C activation processes of all four-membered ring systems. As early as 1964,[130] it was shown that exposure of biphenylene to $Cr(CO)_6$ generated small quantities of fluorenone. Subsequent historical developments have been reviewed,[131] with the focus here on a selection of recent methodologies only.

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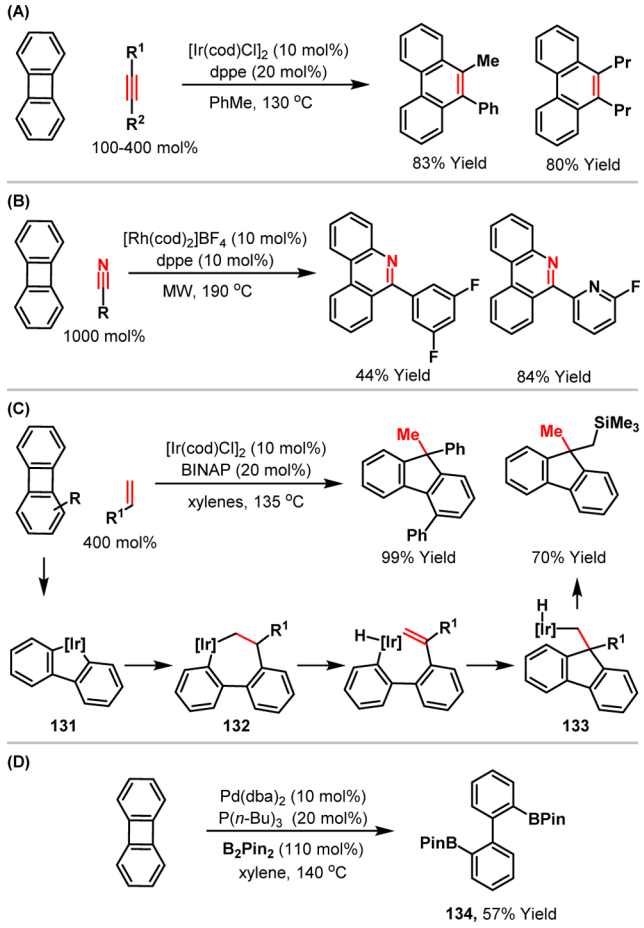
From a synthetic viewpoint, perhaps the most attractive processes are those that involve C−C activation-triggered insertion of C-based units into biphenylenes. Roithová, Kotora, and co-workers[132] have demonstrated efficient Ir(I)-catalyzed insertion of disubstituted alkynes to provide highly conjugated polyaromatic ring systems (Scheme 32A). Vollhardt and co-workers[133] have reported Ni-catalyzed insertion of alkynes into systems possessing multiple biphenylene units. Kotora and co-workers[132,134] also developed Rh-catalyzed insertions of nitriles to provide a flexible approach to substituted phenanthridines (Scheme 32B). Under Ir-catalyzed conditions, Shibata and co-workers[135] showed that insertion of alkenes generates disubstituted fluorenes (Scheme 32C). The proposed mechanism involves insertion of the alkene into initially generated iridacycle **131** to provide **132**. β-Hydride elimination and hydrometalation then generates **133**, which releases the product upon C−H reductive elimination. Processes that introduce heteroatoms have also been reported. Matsuda and Kirikae[136] have shown that, under palladium-catalyzed conditions, hydrometalation or bismetalation of biphenylene can be achieved. For example, treatment of biphenylene with B_2Pin_2, by use of a Pd system modified with $P(n\text{-}Bu)_3$, provided bisborylation product **134** in 57% yield (Scheme 32D). Other examples included hydrosilylations and bis-stannylations.

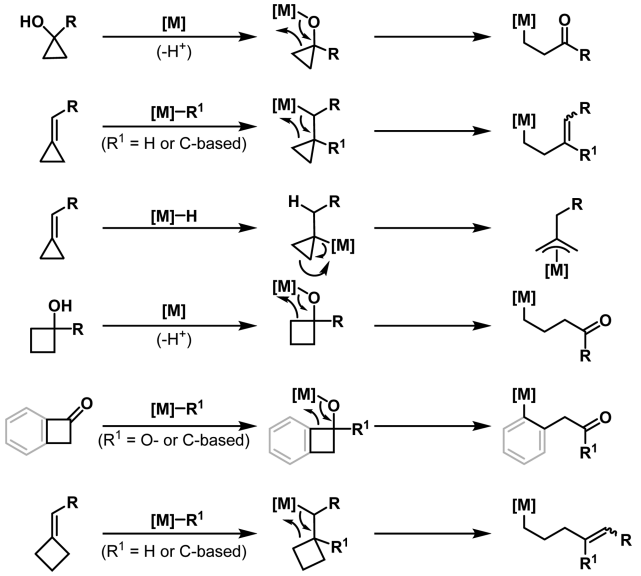
Scheme 32. Selected Recent Methodologies Involving C−C Activation of Biphenylenes



3. β-CARBON ELIMINATION-BASED METHODOLOGIES

The methodologies discussed so far all involve C−C oxidative addition and, as such, can be termed C−C activation processes. Another highly significant family of C−C cleavage reactions is enabled by redox-neutral β-carbon elimination, wherein cleavage of a β-C−C σ-bond occurs with concomitant generation of a π-bond. On first inspection, thermodynamic considerations render such processes unlikely, and as such, special design features are required to facilitate this process. One common manifestation resides in decarboxylative cross-coupling reactions,[137] wherein β-carbon elimination is driven by release of carbon dioxide; however, as already mentioned, processes of this type are outside the immediate focus of this review. The following discussion will instead focus on methodologies where β-carbon elimination is driven by release of ring strain, most commonly from cyclopropane and cyclobutane moieties. A summary of activation strategies that have been employed recently is given in Scheme 33 (see also Scheme 12B,C).

Scheme 33. Strategies for Triggering β-Carbon Elimination Used in Recent Methodologies



3.1. Cyclopropanol-based Processes

Cyclopropanol silyl ethers function as homoenolate equivalents, as demonstrated by Nakamura and Kuwajima in 1977.[138] In Pd catalysis, work by Nakamura and co-workers[139] suggests C−C cleavage by way of corner attack onto the Pd(II) center (**135**) (Scheme 34A). Later, Park and Cha[140] demonstrated that unprotected cyclopropanols could also be engaged in Pd-catalyzed C−C bond cleavage processes. Here, it was proposed that β-carbon elimination from alkoxy intermediates **136** generates alkyl-Pd(II) intermediates **137**. Rosa and Orellana[141] demonstrated inter- and intramolecular processes involving cyclopropanol silyl ethers that are triggered by aryl-Pd(II) intermediates generated from aryl halides (Scheme 34B). Note that tetrabutylammonium fluoride (TBAF) is proposed to effect deprotection to the cyclopropanol in situ, which then enables ligation and C−C cleavage by β-carbon elimination. Cyclopropanols (e.g., **138**) undergo β-carbon elimination, C−H palladation, and reductive elimination to provide oxidative

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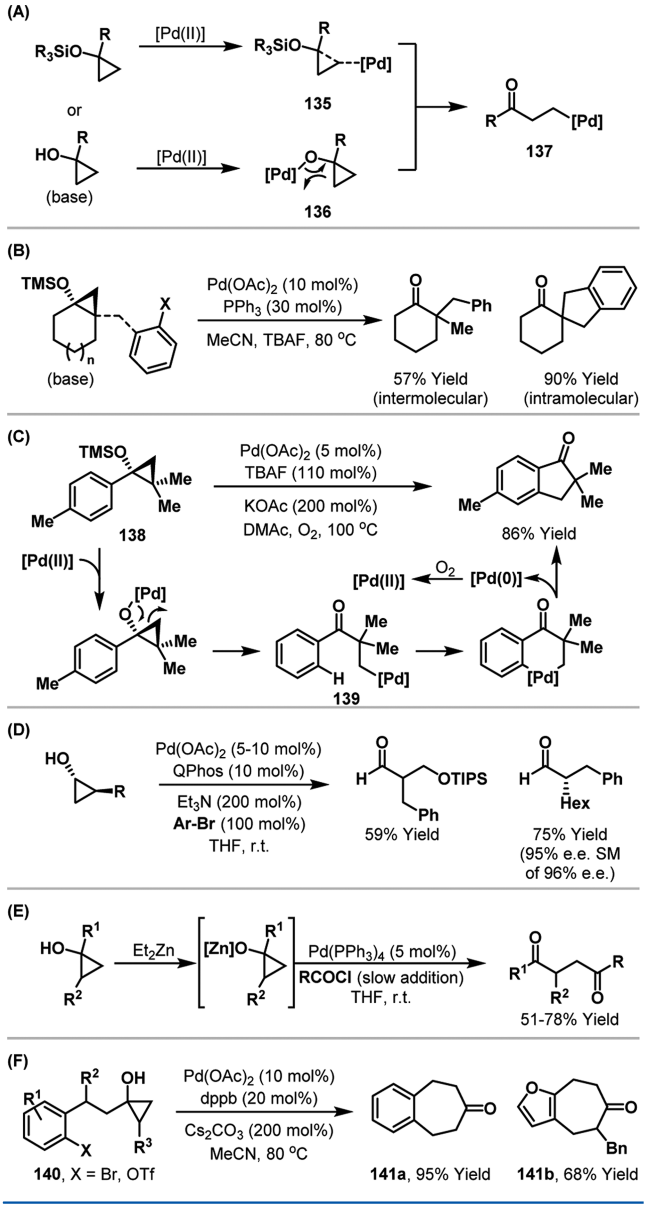
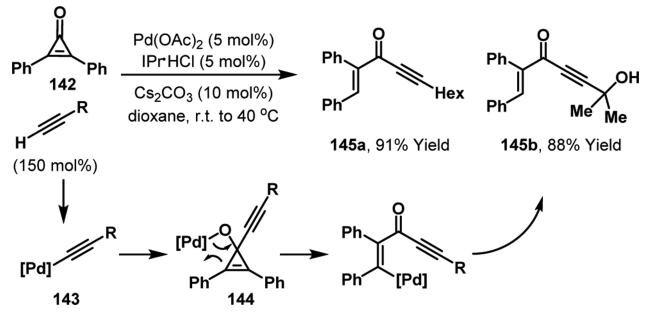
Scheme 34. Cyclopropanols as Homoenolate Equivalents



access to indanones (Scheme 34C).[142] The processes in Scheme 34B,C require alkyl-Pd(II) intermediates (e.g., **139**) that cannot undergo β-hydride elimination and are thus limited to α-trisubstituted products. Cheng and Walsh[143] addressed this issue by reporting a QPhos-enabled system that was effective at room temperature with aryl bromides (Scheme 34D). Use of enantioenriched cyclopropanols provided enantioenriched products with high enantiospecificity. Extension of the activation mode to other classes of electrophile has also been achieved. Cha and co-workers[144] showed that acid chlorides are competent partners for coupling with zinc cyclopropanoxides generated in situ (Scheme 34E). This approach is notable in providing direct access to 1,4-diketones. For cases involving nonsymmetrical cyclopropanols, C−C cleavage is selective for the less hindered proximal C−C bond. The chemistry was later applied to a synthesis of indolizidine 223AB.[145] Related processes have been developed with alkynyl bromides as the electrophile to provide β-alkynylated ketones.[146] Intramolecular variants are particularly powerful for the construction of carbocycles; Ydhyam and Cha[147] showcased this in the construction of challenging seven-membered ring systems (e.g., **141a,b**), where initiation occurs by oxidative addition into pendant aryl or alkenyl (pseudo)-halides **140** (Scheme 34F). Dai and co-workers[148,149] have developed copper-catalyzed conditions that enable trifluoromethylation, thiotrifluoromethylation, and amination of cyclopropanols. Related conditions facilitate radical-based C(sp^3)−C(sp^3) cross-couplings of cyclopropanols.[150]

β-Carbon elimination processes that use highly strained cyclopropenoxides have also been reported recently. Matsuda and Sakurai[151] demonstrated efficient Pd-catalyzed conversion of cyclopropenone **142** and alkynes to yne-enone products (e.g., **145a,b**) (Scheme 35). The reaction is believed to involve

Scheme 35. Pd-Catalyzed Alkynylation of Cyclopropenones



1,2-addition of alkynyl-Pd(II) species **143** to the cyclopropenone carbonyl to afford **144**. This is followed by β-carbon elimination and protodemetalation to release the product. Although the methodology was demonstrated only on cycopropenone **142**, a good range of terminal alkynes could be employed.

3.2. Cyclopropane-based Processes

Alkylidenecyclopropanes are also a common substrate class for β-carbon elimination processes, providing complementarity to the C−C activation methodologies discussed in section 2.2.[21−23] A range of recent reports have exploited hydrometalation of the alkene unit to set up the β-carbon elimination step. Simaan and Marek[152] demonstrated hydroformylative conversion of alkylidenecyclopropanes **146** to γ,δ-unsaturated aldehydes (e.g., **149a,b**) bearing β-quaternary stereocenters (Scheme 36A). An example using an enantiopure substrate provided the product with high levels of enantiospecificity. The proposed mechanism invokes initial hydrometalation of the alkene unit to generate **147**, which undergoes β-carbon elimination to alkyl-Rh(I) species **148**. Subsequent carbonylation is followed by capture of dihydrogen and reductive elimination to release the product. Aïssa and co-workers[153] developed an elegant approach to seven-membered rings based on intramolecular Rh-catalyzed hydroacylation of alkylidenecyclopropanes (Scheme 36B). Here, C−H oxidative addition generates **150**, with subsequent hydrometalation, β-carbon elimination, and C−C reductive elimination providing cycloheptenone products (e.g., **151a,b**) bearing quaternary stereocenters. Bidirectional variants were also disclosed, and it was shown that the alkylidenecyclopropane reacted preferentially to other pendant unsaturated moieties, such as alkenes and alkynes. The regioselectivity of the hydrometalation step for the processes in Scheme 36A,B is such that the metal ends up distal to the cyclopropane. Processes involving hydrometalation in the opposite direction have also been developed. Mascareñas,

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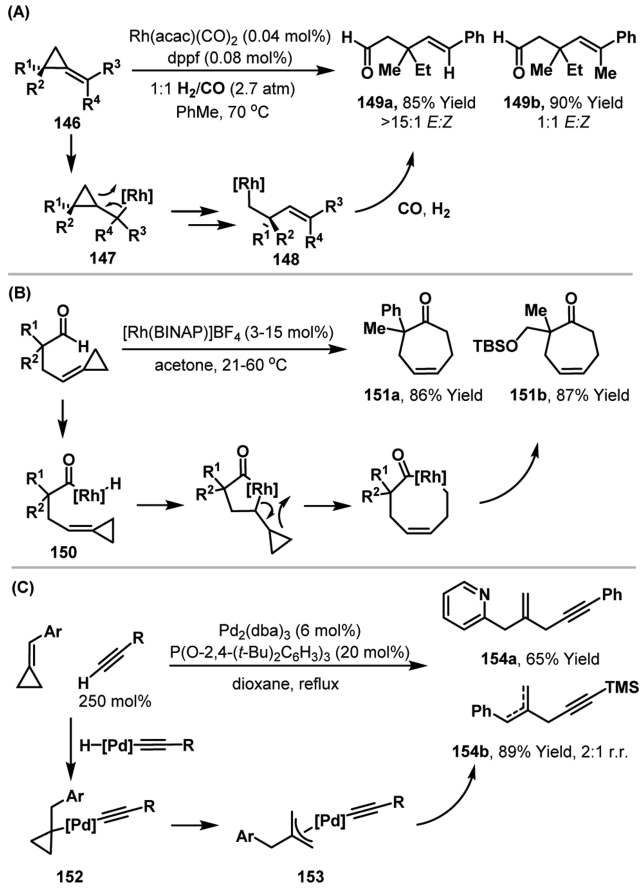
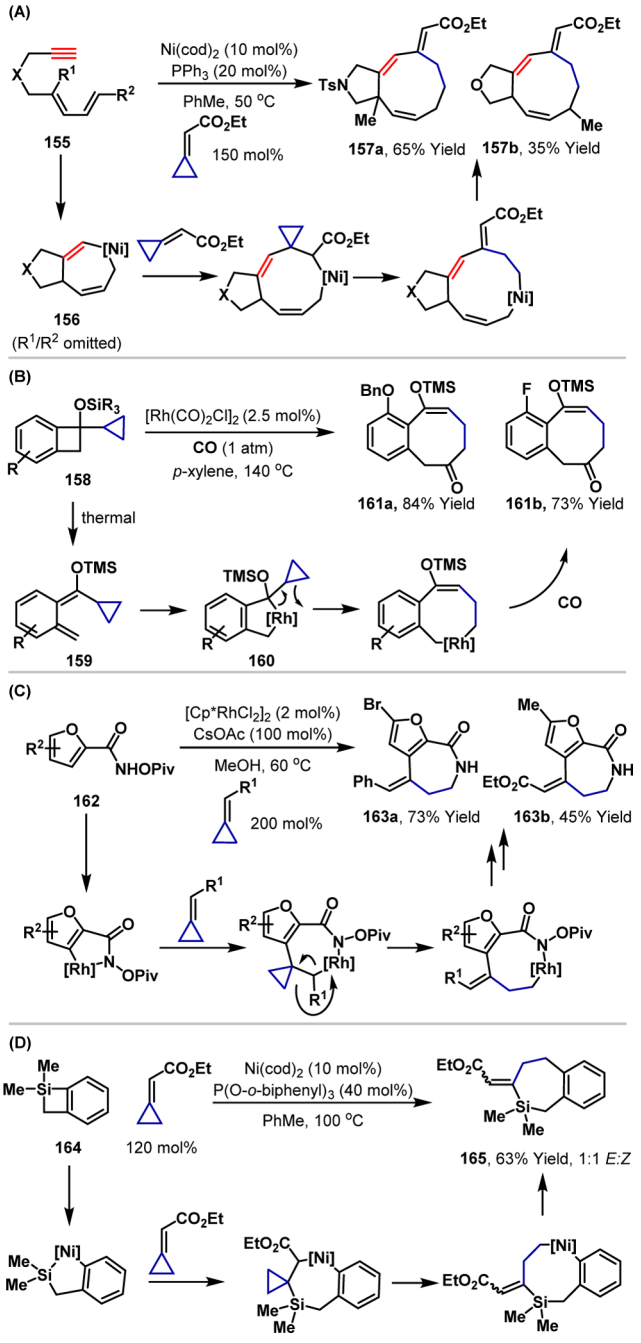
Scheme 36. β-Carbon Elimination of Cyclopropyl Moieties Triggered by Hydrometalation



López, and co-workers[154] showed that catalytically generated alkynyl-Pd(II) intermediates can be used to provide skipped enynes (e.g., **154a,b**), with good to moderate levels of regiocontrol (Scheme 36C). Here, hydrometalation of the alkylidenecyclopropane provides Pd(II) intermediate **152**, which undergoes β-carbon elimination via the distal cyclopropane bond to generate π-allyl **153**. C−C reductive elimination then provides the products.

Carbometalation can also be used to setup the β-carbon elimination step. This, in principle, allows reactions to be designed around any catalytically generated organometallic species that can undergo alkene migratory insertion. For example, Saito et al.[155] outlined an impressive approach to nine-membered carbocycles, involving Ni-catalyzed union of yne-dienes and polarized alkylidenecyclopropanes (Scheme 37A). The reaction likely commences with oxidative cyclization of yne-dienes **155** to provide nickelacycles **156**. 1,2-Carbometalation of the alkylidenecyclopropane is followed by β-carbon elimination and C−C reductive elimination to provide the products (e.g., **157a,b**). This process demonstrates the value of using β-carbon elimination from a small ring system to build challenging medium-ring carbocycles. An alternative approach by Yu and co-workers[156] generated embedded alkylidenecyclopropanes **159** by thermal ring opening of benzocyclobutenes **158** (Scheme 37B). Oxidative capture of **159** by a Rh(I) catalyst generates rhodacycles **160**, which undergo β-carbon elimination, carbonylation (not depicted), and C−C reductive elimination to provide benzofused eight-membered rings (e.g., **161a,b**). C−H

Scheme 37. β-Carbon Elimination of Cyclopropyl Moieties Triggered by Carbometalation and Related Processes



activation processes have also been used as starting points. Cui et al.[157] demonstrated conversion of furan systems **162** and alkylidenecyclopropanes to seven-membered furanolactams (e.g., **163a,b**), via initial cyclometalation using a Rh(III) catalyst (Scheme 37C); note that the N−O bond acts as an internal oxidant and this reaction pathway was not observed for less electron-rich arenes. More exotic metallacyclic intermediates have also been exploited. Under Ni-catalyzed conditions, Saito et al.[158] showed that a sequence of C−Si oxidative addition and silylmetalation could be used to convert benzosilacyclobutenes **164** and polarized alkylidenecyclopropanes to benzofused silacycles (e.g., **165**) (Scheme 37D).

The methodologies in Scheme 37 all involve β-carbon elimination from bicyclic metallacycles en route to bicyclic

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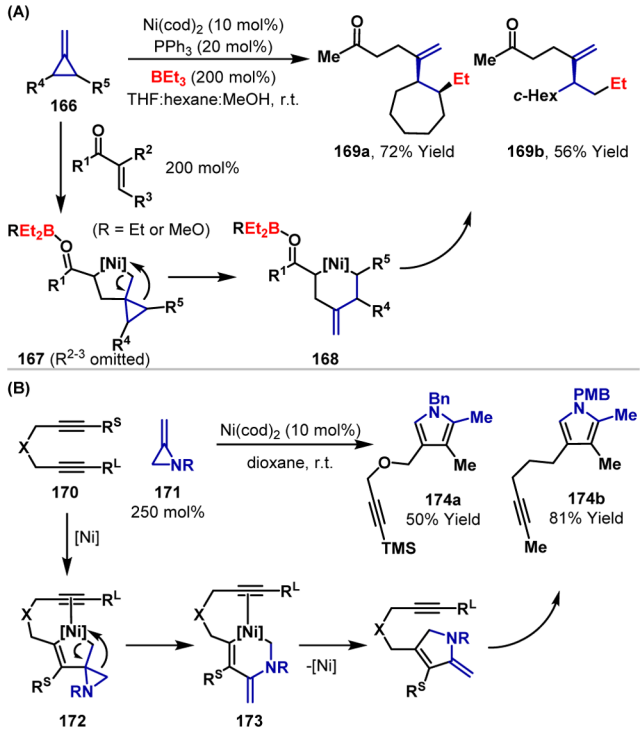
products. Under Ni-catalyzed conditions, methodologies have been developed that provide access to metallamonocyclic β-carbon elimination precursors. By use of BEt_3 as the terminal reductant, Ni-catalyzed coupling between alkylidenecyclopropanes **166** and enones generates 1,1-disubstituted alkenes (e.g., **169a,b**), as demonstrated by Ogata et al.[159] (Scheme 38A).

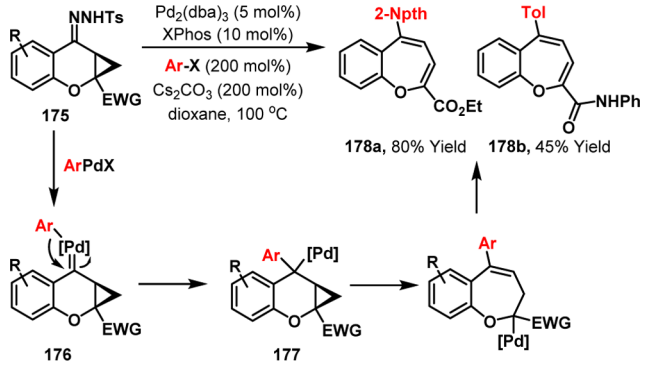
Scheme 38. β-Carbon Elimination of Cyclopropyl and Aziridinyl Moieties Triggered by Oxidative Coupling



The protocol offers good scope for accessing challenging motifs, with the mechanism likely proceeding via β-carbon elimination from nickelacycles **167**. This generates **168**, which is reduced by the $BREt_2$ moiety to release the products. An earlier report detailing the synthesis of O-silyl allylic ethers by Ni-catalyzed multicomponent coupling of alkylidenecyclopropanes, aldehydes, and silanes is also of note.[160] An interesting extension to this area was reported by Wan and co-workers,[161] who developed a pyrrole synthesis by combining methylene aziridines **171** with diynes **170** (Scheme 38B). Here, generation of nickelacyclopentene **172** is followed by preferential β-carbon elimination (rather than β-nitrogen elimination) to afford **173**. C−C reductive elimination and isomerization provides the products (e.g., **174a,b**). The process requires diyne substrates, with stabilizing coordination of the spectator alkyne invoked as a key factor.

C−C bond-forming carbene rearrangements have also been used as the basis for β-carbon elimination methodologies (Scheme 39). Zhou and co-workers[162] showed that tosyl hydrazones **175**, containing a neighboring cyclopropane, are converted to benzoxepines (e.g., **178a,b**) upon exposure to Pd(0) catalysts and aryl (pseudo)halides. The mechanism commences with conversion of **175** to Pd-carbene **176**, via a catalytically generated aryl-Pd(II) intermediate. 1,2-Migration of the arene provides benzylic-Pd species **177**, which undergoes β-carbon elimination and β-hydride elimination to release the product.

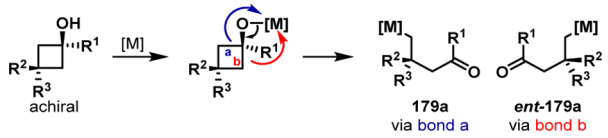
Scheme 39. β-Carbon Elimination Triggered by Pd-Catalyzed Carbene Migratory Insertion



3.3. Cyclobutanol-based Processes

The β-carbon elimination processes highlighted so far all involve three-membered rings. However, β-carbon elimination is not limited to strained systems. Indeed, β-carbon elimination of aryl moieties from acyclic benzylic tertiary alkoxides is a reasonably facile process.[163] As such, β-carbon elimination processes are readily extended to cyclobutane ring systems; this contrasts C−C activation methodologies, where activated ring systems are required. Perhaps the most common approach has been to use cyclobutanols as substrates for such processes, with impressive enantioselective methodologies developed prior to 2009 under Rh- or Pd-catalyzed conditions.[164,165] The general strategy is shown in Scheme 40, wherein ligation of the

Scheme 40. C−C Cleavage via Metal-Catalyzed β-Carbon Elimination of Cyclobutanols



substrate (which may be generated in situ)[165] to the metal center precedes C−C bond cleavage by β-carbon elimination to generate an alkyl-metal intermediate (**179a**). Productive deployment of this activation mode requires the design of reactions that trap this species in subsequent bond-forming processes. As will be seen, the use of chiral ligands allows for selection of one of the two enantiotopic C−C bonds to generate products containing defined quaternary stereocenters.

Perhaps the simplest manifestation of the activation mode outlined in Scheme 40 is in processes where the alkyl-metal intermediate undergoes protodemetalation. In 2010, Seiser and Cramer[166] reported asymmetric reactions of this type, wherein a Rh(I)-catalyst modified with DTBM-SEGPHOS delivered target ketones **182** in high yield and enantioselectivity (Scheme 41). Note that the same enantiomer of the product can be generated from either the *trans*- or *cis-tert*-cyclobutanols simply by switching the enantiomeric form of the ligand. Deuterium labeling studies revealed that protodemetalation does not occur directly from intermediate **180**, which instead undergoes a [1,3]-Rh shift prior to protonation of Rh-enolate **181**. The chemistry was applied to a synthesis of (*S*)-4-ethyl-4-methyloctane, the simplest unbranched saturated hydrocarbon with a quaternary stereocenter.

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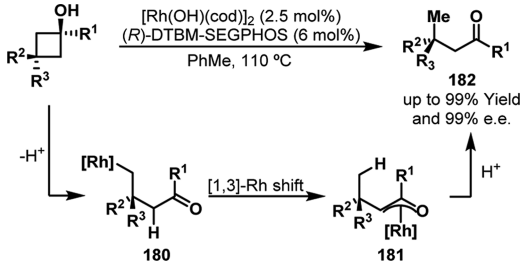
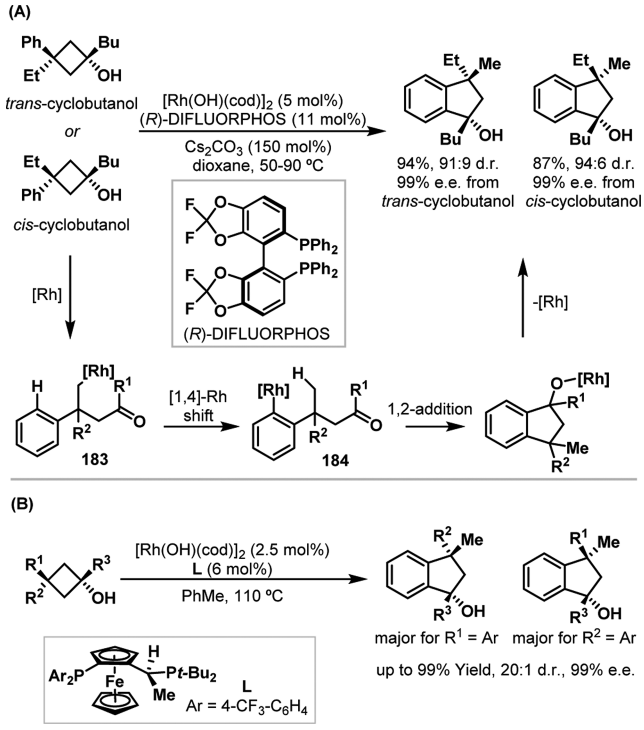
Scheme 41. Enantioselective Synthesis of Quaternary Stereocenters by β-Carbon Elimination from Cyclobutanols



The process in Scheme 41 is predated by reports in 2009 from Cramer and co-workers[167] and Murakami and co-workers,[168] which outlined 1,4-Rh shifts from intermediates **183**. This provided the basis for an enantioselective entry to indanols (Scheme 42). Both groups reported that the process is

Scheme 42. Enantioselective Synthesis of Indanols[a]

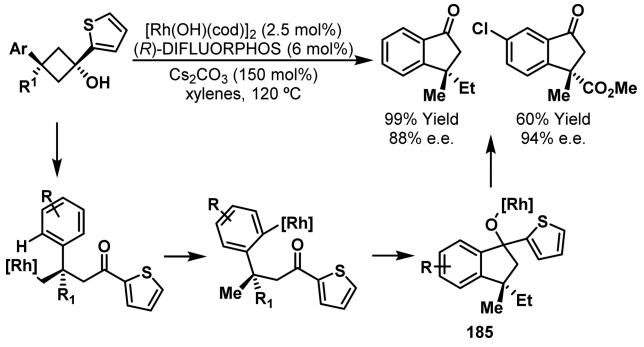


[a]As reported by (A) Murakami and co-workers[168] and (B) Cramer and co-workers.[167]

diastereospecific; thus the relative configuration of the product can be changed by switching from a *cis*- to a *trans*-cyclobutanol. The process commences with enantioselective desymmetrization of the cyclobutanol to generate alkyl-Rh(I) species **183** (Scheme 42A). This then undergoes a [1,4]-Rh shift onto the aryl moiety to generate aryl-Rh(I) species **184**, which is trapped by 1,2-addition onto the ketone. Murakami's studies indicate that the formation of both stereocenters is under catalyst control, such that the quaternary stereocenter of **184** (determined by enantioselective C−C bond cleavage) has minimal influence on the diastereoselectivity of 1,2-addition. Because this step is highly controlled, the relative stereochemistry of the starting material influences which diastereomer of the product is formed.

By replacing the R^3 group with an aryl moiety (see Scheme 42B), Cramer and co-workers[169] expanded the scope of the process to the enantioselective synthesis of indanones (Scheme 43). In these cases, a second β-carbon elimination at the stage

Scheme 43. Synthesis of Indanones[a]

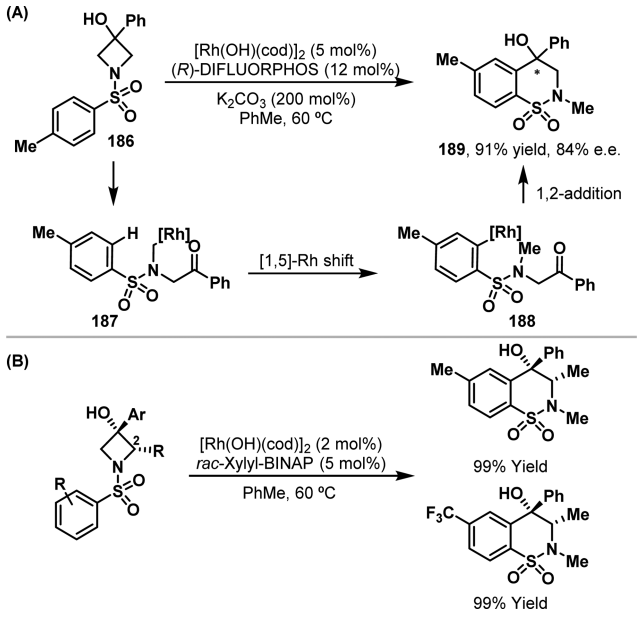


[a]As reported by Cramer and co-workers.[169]

of **185** releases the product and an aryl-Rh(I) species; presumably, it is this species that undergoes protodemetalation to close the catalytic cycle. The process is most efficient when the aryl moiety is electron-rich, and from a survey of different groups, a 2-thienyl moiety was found to be most effective. Related indanones are also accessible via a distinct C−C activation methodology reported by Murakami and co-workers in 2006.[170]

Subsequently, processes involving [1,5]-Rh shifts after β-carbon elimination (rather than [1,4]-shifts) were developed. Murakami and co-workers[171] showed that rearrangement of azetidin-3-ols (e.g., **186**) led to benzosultams (e.g., **189**) in high yield (Scheme 44A). Here, β-carbon elimination generates alkyl-Rh intermediate **187**, which is predisposed to C(sp^2)−H activation of the arene to generate **188**. 1,2-Addition and protodemetalation then provides the product in high enantioselectivity. High diastereoselectivities were observed for azetidinols possessing substitution at C2 (Scheme 44B), and

Scheme 44. Synthesis of Benzosultams from Azetidinols



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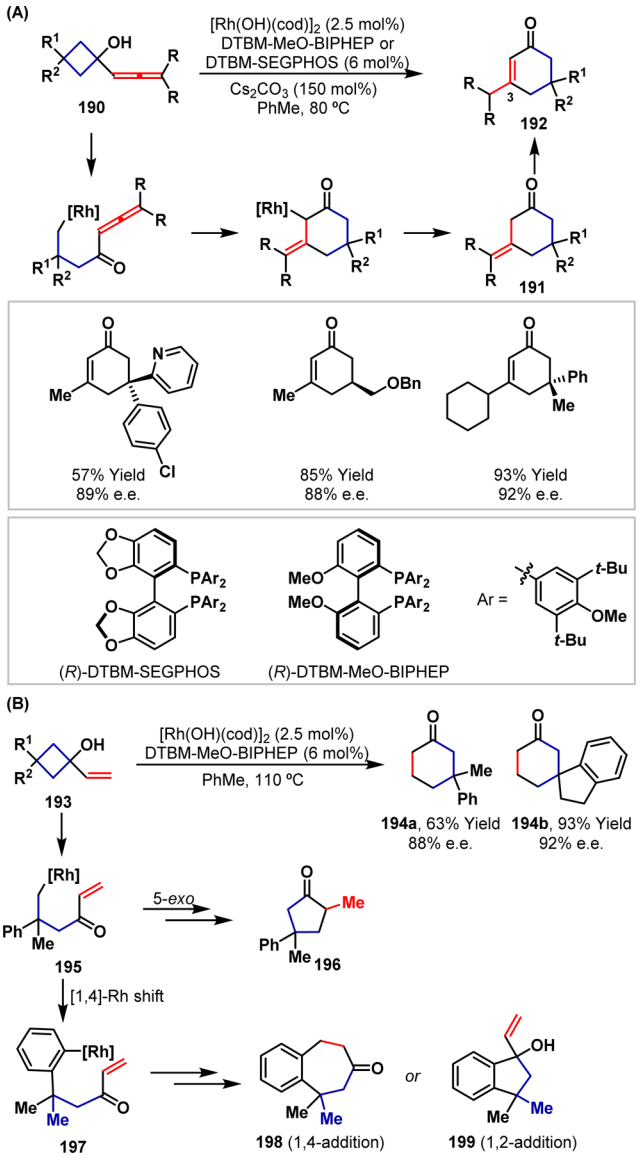
a diastereoselection model was proposed. Note that for C2-substituted systems, the β-carbon elimination event is highly selective for the less hindered C−C bond and complete retention of predefined stereochemistry was observed (i.e., the processes are enantiospecific).

In the methodologies outlined so far, C−C activation is used to generate alkyl- or aryl-Rh(I) intermediates which then form a new C−C bond by 1,2-addition onto a carbonyl group. Seiser and Cramer[172] have shown that the use of allylic *tert*-cyclobutanols enables complementary access to six-membered rings; here, C−C bond formation occurs via 1,4-addition onto an enone generated in situ (Scheme 45A). In initial studies, it

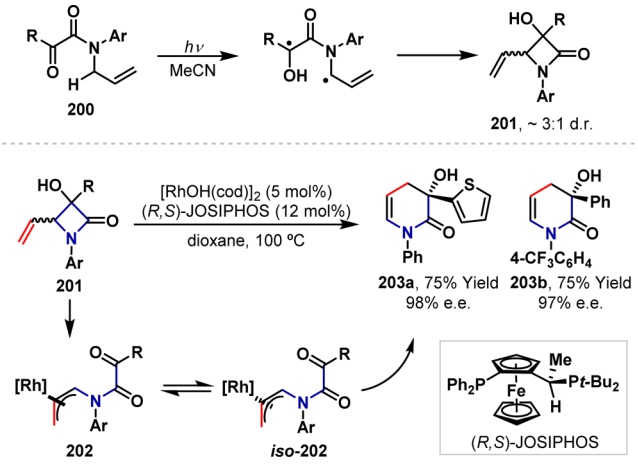
Scheme 45. Synthesis of Cyclohexenones and Cyclohexanones from Cyclobutanols



was shown that allene-based systems **190** reacted effectively to provide cyclohexenone products **192** via isomerization of initially formed β,γ-unsaturated systems **191**. Enantioselective variants were achieved with a variety of chiral ligand systems, with 2,2′-bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)-phosphino]-6,6′-dimethoxy-1,1′-biphenyl (DTBM-MeO-BIPHEP) and DTBM-SEGPHOS emerging as the most general. The protocol shows excellent scope, although only processes that introduced methyl, cyclohexyl, and isopropyl groups in the C3 position of **192** were demonstrated. By omitting Cs_2CO_3, olefin isomerization could be suppressed such that the initially generated β,γ-enones could be isolated. In situ Rh-catalyzed rearrangement−reduction sequences were also demonstrated to provide access to more stereochemically complex cyclohexanes. Extension of the approach to alkenes **193** was challenging because several distinct reaction pathways became competitive (Scheme 45B). In addition to the desired 1,4-addition process (**193** to **194a,b**), alkyl-Rh intermediate **195** could undergo 5-exo ring closure, leading to **196**. Alternatively, a [1,4]-Rh shift could generate aryl-Rh intermediate **197**, which engages the enone in either 1,4- or 1,2-addition to provide either benzocycloheptenone **198** or indanol **199**. It was found that DTBM-MeO-BIPHEP improved the selectivity for cyclohexanone products, and by combining this with favorable substrate classes, the targets could be formed in good selectivity, yield, and enantioselectivity.

The processes in Scheme 45 employ strained allylic alcohols, but interesting reactivity can also be achieved by use of homoallylic systems. β-Lactam-based alcohols **201** are readily available by Norrish−Yang-type photocyclization[173] of *N*-allylglyoxylamides **200** (Scheme 46). Subjection of these to

Scheme 46. Piperidinones via Sequential Light- and Rh-Promoted Processes



Rh(I) systems effects β-carbon elimination to nucleophilic Rh(I) allyls **202**/*iso*-**202**, which engage the highly activated ketone group in a 1,2-addition step to provide, ultimately, piperidinones (e.g., **203a,b**).[174] Starting materials **201** are formed as a mixture of diastereomers but this was inconsequential to enantioselective variants, which were achieved by use of (*R*)-1-[(S_P)-2-(diphenylphosphino)-ferrocenyl]ethyldi-(*tert*-butyl)phosphine [(*R*)-JOSIPHOS] as ligand. Here, the fluxional nature of allyl-Rh species **202**/*iso*-**202**, which can equilibrate via the η^1 form, enables both diastereomeric starting materials to converge to the same intermediate, such that high enantioselectivity can be obtained from both. The methodology is notable because it harnesses molecular strain installed by the photochemical step to enable a subsequent C−C activation process. The net result is a short and byproduct-free entry to valuable heterocyclic ring systems.

By combining the β-carbon elimination step with a subsequent C−X oxidative addition step, rhodaindanes can be generated and harnessed. In one manifestation of this concept,

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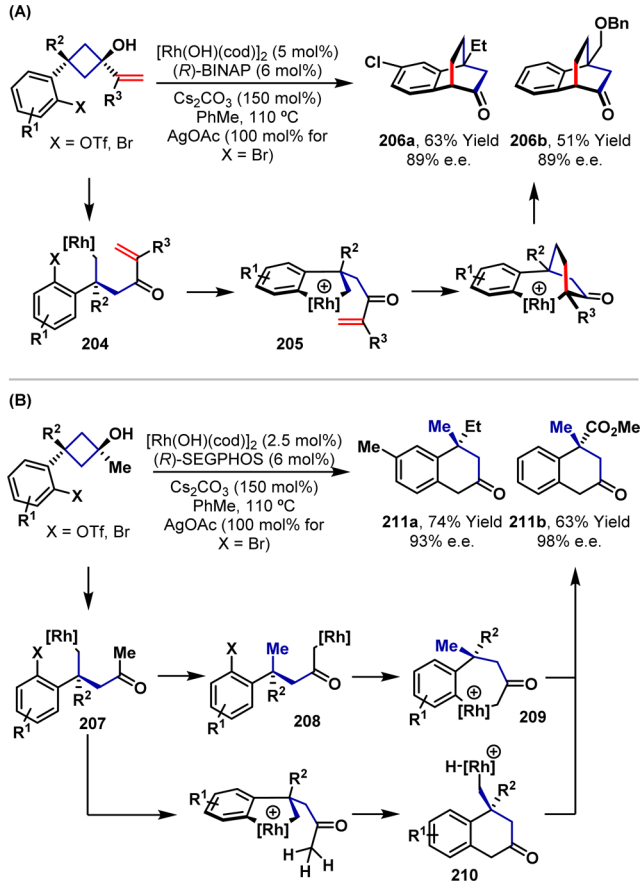
Souillart and Cramer[175] showed that rhodacycles **205** lead to challenging bridged systems (e.g., **206a,b**) via carbometalation of the enone generated in situ and subsequent C−C reductive elimination (Scheme 47A). The reaction conditions were

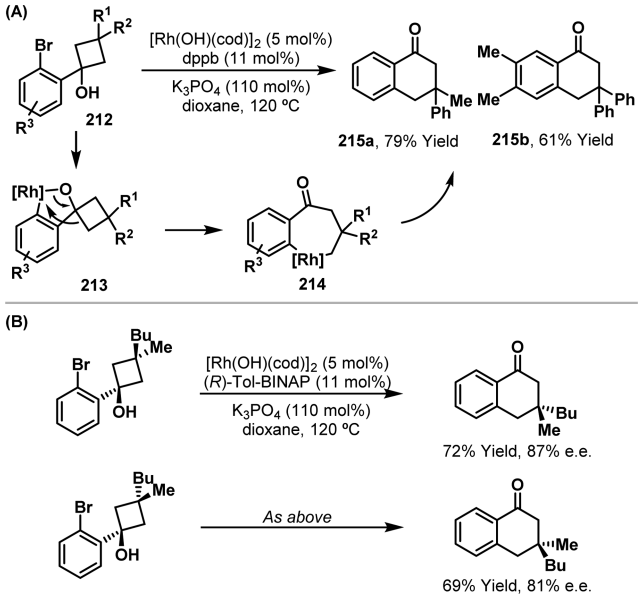
Scheme 47. Synthesis of (A) Bridged Ring Systems and (B) β-Tetralones from Cyclobutanols



optimized both for high enantioselectivity and to suppress an enone aryl-metalation pathway, which is also accessible from **205**. For nonallylic *tert*-cyclobutanols, β-carbon elimination is followed by C−X oxidative addition and C−C formation via σ-bond metathesis to generate alkyl-Rh intermediates **210** (Scheme 47B). These undergo protodemetalation to release the product (e.g., **211a,b**). Alternatively, **207** may undergo a [1,5]-Rh shift to generate primary alkyl-Rh intermediates **208**. These can then undergo C−X oxidative addition (to **209**) prior to C−C reductive elimination. Souillart and Cramer[175] outlined the scope of this process and demonstrated high enantioselectivities using (*R*)-SEGPHOS as ligand. The reaction is limited to α-methylcyclobutanols because of limitations associated with the σ-bond metathesis step.

The studies outlined in Scheme 47 are predated by a report from Murakami and co-workers,[176] which demonstrated conceptually distinct C−X activation β-carbon elimination sequences (Scheme 48A). Here systems **212**, bearing a pendant ortho-brominated arene, undergo alkoxy-directed C−Br oxidative addition to provide rhodacycles **213**. At this stage, facile β-carbon elimination drives formation of seven-membered rhodacycle **214**, which, upon C−C reductive elimination, provides α-tetralones (e.g., **215a,b**). An example involving an azetidin-3-ol was also reported, which provided a

Scheme 48. α-Tetralones by a C−Br/β-Carbon Elimination Sequence



benzofused piperidin-3-one product. The process is efficient for both electron-rich and electron-poor arenes, and enantioselective variants were demonstrated by use of (*R*)-Tol-BINAP as ligand (up to 87% ee) (Scheme 48B). Note that enantioselection in these cases occurs at the stage of Rh(III) intermediate **213** (cf. Scheme 47) and the two diastereomers of the starting material provide opposite enantiomers of the product from the same antipode of the chiral ligand.

The C−C bond-forming processes outlined so far involve intramolecular trapping of an organo-Rh intermediate. Recently, intermolecular processes have also been realized, suggesting a potentially wider role of metal-catalyzed C−C cleavage in byproduct-free fragment union reactions. Murakami and co-workers[177] have shown that alkyl-Rh intermediates **217** can be trapped by isocyanates to provide C-carbamoylation products (Scheme 49A). The reaction is notable because competing O-carbamoylation of **216** is avoided. An enantioselective variant was also demonstrated (Scheme 49B).

Formal cycloaddition processes are possible by trapping cyclobutanol-derived alkyl-Rh intermediates with exogenous diazo compounds (Scheme 50A).[178] Here, intermediates **218** are intercepted by diazo species **219**, generated in situ, to provide Rh-carbenes **220**. At this stage, [1,2]-migration of the alkyl group occurs to provide secondary alkyl-Rh intermediates **221**. These undergo 5-exo-cyclization with the ketone generated in situ, and subsequent alkoxy exchange with further cyclobutanol releases the product (**222**). By use of different chiral ligands, excellent yields, good diastereoselectivities, and excellent enantioselectivities can be achieved. For the processes in Scheme 50B, diastereoselectivity is determined by differentiation of the two π-faces of the carbonyl group during ring closure, whereas enantioselectivity is defined by the [1,2]-migration step. In Scheme 50C, the situation is more complex, with the chiral ligand controlling both the β-carbon elimination and [1,2]-migration steps. The approach provides stereocontrolled access to highly complex cyclopentane ring systems.

Murakami and co-workers[179] have shown that β-carbon elimination of benzocyclobutenols **223** is selective for the C(sp^2)−C(sp^3) bond to generate aryl-Rh intermediates **225**

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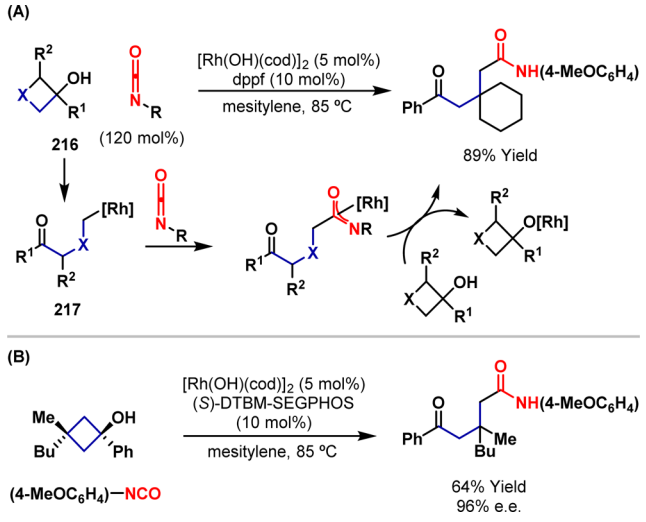
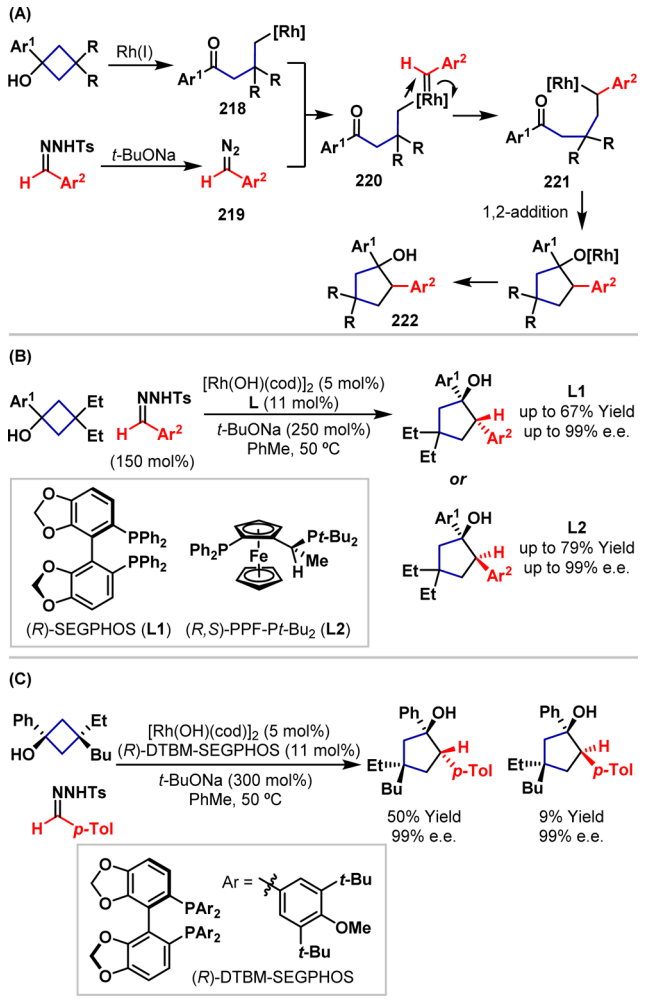
Scheme 49. β-Carbon Elimination-Triggered C-Carbamoylation

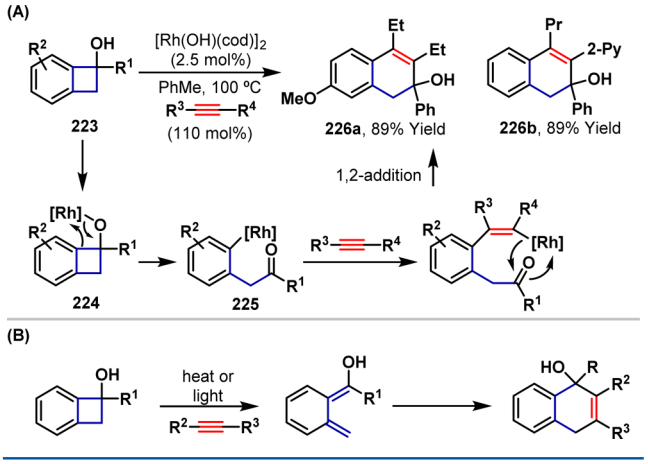


Scheme 50. β-Carbon Elimination−Carbene Insertion Cycloadditions



(Scheme 51A). These can then be trapped by alkynes en route to benzocyclohexenol products (e.g., **226a,b**). Computational studies suggest that coordination of Rh to the arene at the stage of **224** provides the selectivity for C−C cleavage.[180] Note that

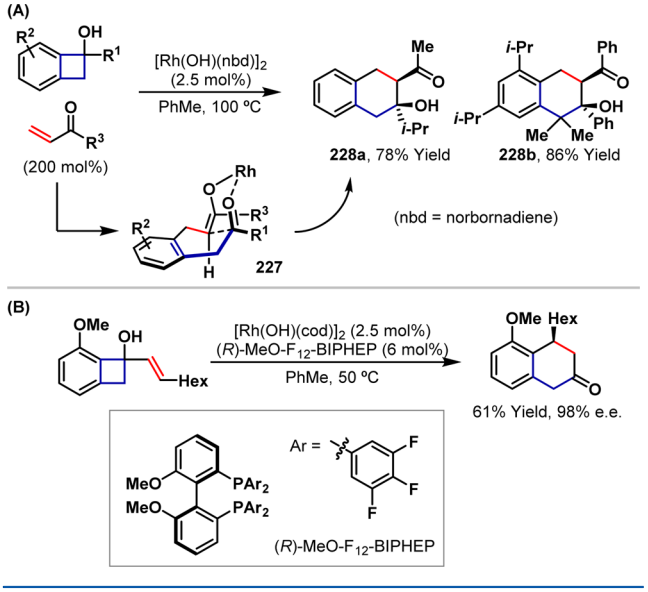
Scheme 51. β-Carbon Elimination-Triggered (4 + 2) Cycloadditions



the method offers complementary regioselectivity to thermally[181] or photochemically[182] driven retrocycloaddition−cycloaddition processes (Scheme 51B). Recently, He and co-workers[183] reported similar processes using allenes in place of alkynes, which, in turn, leads to products with exocyclic alkenes. In related work, Matsuda and Miura[184] demonstrated formal cycloadditions between cyclobutenols and alkynes.

Other classes of intermolecular reaction have been developed. For example, Murakami and co-workers[185] have shown that trapping of β-carbon elimination-derived aryl-Rh intermediates **225** with enones provides Rh-enolates **227** (Scheme 52A). These engage the ketone generated during the

Scheme 52. β-Carbon Elimination-Triggered Conjugate Addition Reactions



β-carbon elimination step in an aldol reaction, which proceeds via the indicated chairlike transition state to afford the products (e.g., **228a,b**) in high diastereoselectivity. In the absence of an enone, β-carbon elimination triggered enantioselective rearrangements were also disclosed (Scheme 52B).

An interesting extension of this chemistry involves its application to the diastereocontrolled synthesis of metacyclophanes possessing planar chirality (Scheme 53).[186] Substrates

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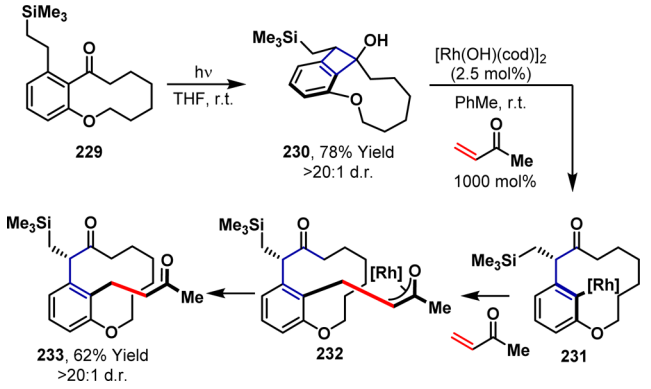
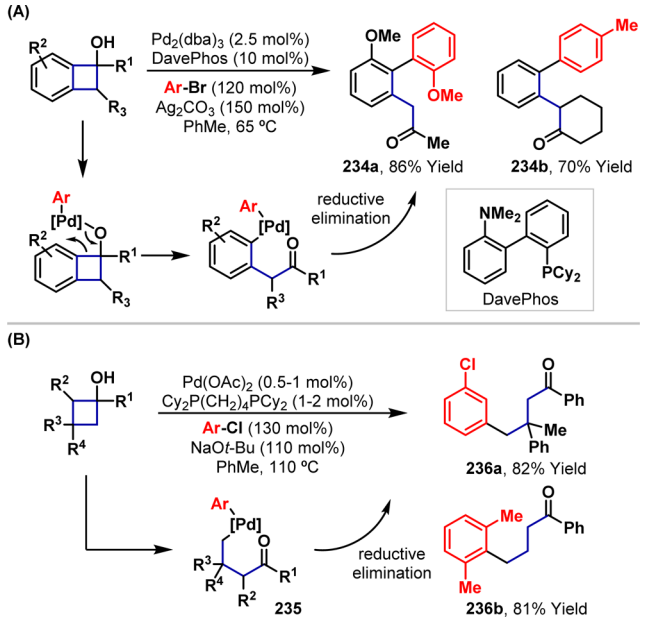
Scheme 53. Photocycloaddition–β-Carbon Elimination Sequence to Diastereomerically Pure Metacyclophanes



230 are accessible in diastereomerically pure form by photocyclization of **229**. The β-carbon elimination step is stereospecific, transferring the relative stereochemistry of **230** to aryl-Rh(I) intermediate **231**. This engages the exogenous enone in a 1,4-addition step to provide, after protodemetalation of **232**, product **233**.

The examples given so far in this section involve Rh-based catalysts; however, there have also been significant developments with Pd systems. Orellana and co-workers[187] have shown that exposure of benzocyclobutenols to aryl-Pd(II) intermediates, generated in situ, leads to a sequence of β-carbon elimination and C–C reductive elimination to provide ortho-arylated products (e.g., **234a,b**) (Scheme 54A). The methodology was applied to the synthesis of phenanthrenes and cyclic imines by designing in situ condensations of the products. Ziadi and Martin[188] demonstrated related processes using cyclobutanols to provide a concise entry to γ-arylated ketones bearing quaternary stereocenters (**236a**) (Scheme 54B). The catalyst system was also uniquely effective at suppressing competing β-hydride elimination at the stage of **235** for the synthesis of C3-monosubstituted systems (**236b**). Note that this approach uses the cyclobutanol as a formal bis-(homoenolate) (cf. section 3.1).

Scheme 54. Pd-Catalyzed β-Carbon Elimination-Triggered Arylation Reactions

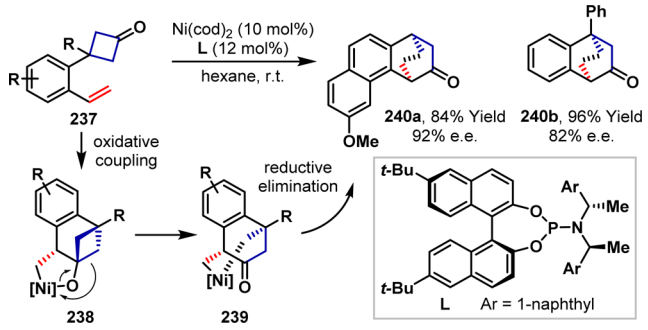


3.4. Cyclobutanone- and Benzocyclobutenone-based Processes

Under Ni-catalyzed conditions, cyclobutanone-based substrates can engage in oxidative coupling processes to generated nickelacycles, which are predisposed to β-carbon elimination. This provides a complementary approach to several of the C–C bond activations outlined in section 2.6.

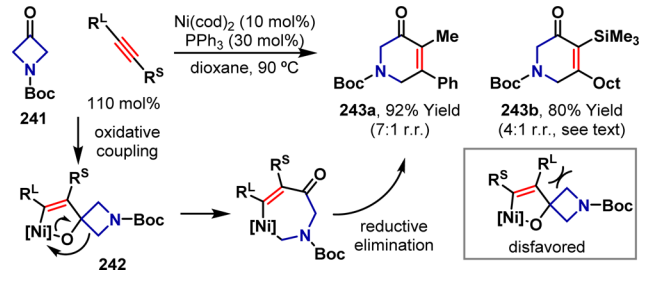
In 2012, building on earlier work,[189,190] Murakami and co-workers[191] reported enantioselective intramolecular Ni-catalyzed (4 + 2) cycloadditions of cyclobutanones **237** bearing pendant styrenes (Scheme 55). Oxidative coupling of the ketone and alkene generates oxanickelacyclopentanes **238**, which undergo stereoselective β-carbon elimination (to **239**) and C–C reductive elimination to provide benzobicyclo[2.2.2]-octenone ring systems (e.g., **240a,b**). More heavily substituted alkenes were not tolerated, presumably due to their increased steric demands. The approach provides direct access to a challenging yet biologically relevant class of ring system.

Scheme 55. Oxidative Coupling–β-Carbon Elimination Sequence to Benzobicyclo[2.2.2]octenones



Intermolecular processes have been developed that use alkynes as a coupling partner. Ho and Aïssa[192] showed that 3-azetidinones **241** and internal alkynes will combine to afford α,β-unsaturated piperidin-3-ones (e.g., **243a,b**) in high yield and good regioselectivity (Scheme 56). At the stage of nickelacycles **242**, steric effects favor an arrangement wherein the larger substituent of the alkyne is placed closer to the Ni center. For systems where R^1 or R^2 = silyl, electronic effects overturn this selectivity. Related 3-oxetanone-based processes were also disclosed. This report was followed quickly by similar studies from Kumar and Louie[193] and Murakami and co-

Scheme 56. Oxidative Coupling–β-Carbon Elimination Sequence to Piperidine Rings[a]



[a]Ho and Aïssa.[192]

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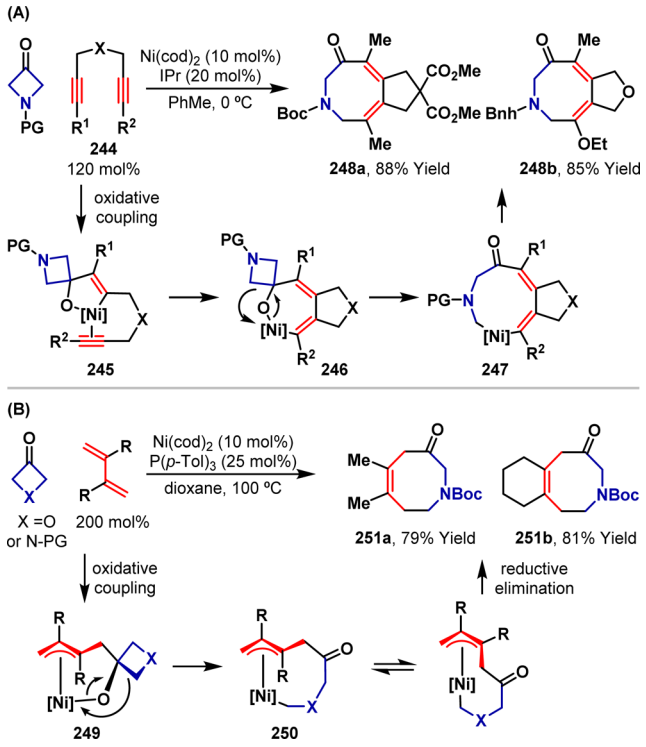
workers,[194] with the latter focusing on 2-substituted 3-azetidinones. In these cases, β-carbon elimination was selective for the less hindered C−C bond and complete retention of C2 stereochemistry was observed. The oxidative coupling mechanisms in Schemes 55 and 56 are supported by related stoichiometric studies.[195,196] Nevertheless, it should be noted that computational studies from Li and Lin[197] do not support an oxidative coupling pathway for the process in Scheme 56, with calculations instead suggesting initiation by C(sp^3)−acyl oxidative addition (cf. Scheme 26). Recently, Harrity and co-workers[198] developed Ni-catalyzed couplings of cyclobutenones and alkynes for the synthesis of phenols; a mechanism analogous to that shown in Scheme 56 was proposed as one possible option.

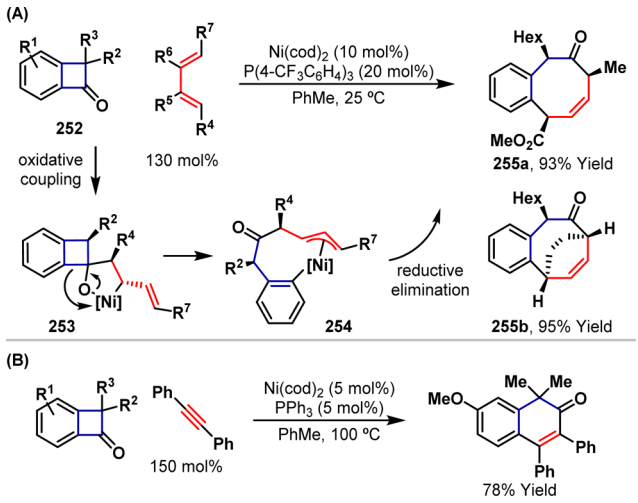
Louie and co-workers[199] have reported (4 + 2 + 2) cycloadditions between 3-azetidinones and diynes **244** to generate fused azocane ring systems (e.g., **248a,b**) (Scheme 57A). At the stage of initially generated oxanickelacyclopentenes **245**, insertion of the tethered alkyne occurs to provide intermediates **246**. β-Carbon elimination to **247** and C−C reductive elimination then follow to release the product. Subsequent studies outlined the design of processes involving 1,3-dienes to provide mono- and bicyclic eight-membered rings (e.g., **251a,b**) (Scheme 57B).[200] Here, the oxidative coupling event generates Ni-allyl intermediate **249**, from which β-carbon elimination occurs to provide **250**. Isomerization and C−C reductive elimination then delivers the products. For C2-substituted 3-azetidinones, erosion of enantiopurity was observed due to Ni-catalyzed epimerization of the starting material. O-based systems (not depicted) can be accessed by use of 3-oxetanones. These methodologies demonstrate once again the utility of β-carbon elimination in the design of medium-ring-forming methodologies.

Scheme 57. Oxidative Coupling−β-Carbon Elimination Approaches to Medium-Ring Heterocycles



Martin and co-workers[201] have exploited Ni-catalyzed cycloadditions of benzocyclobutenones to gain access to benzofused eight-membered rings (Scheme 58A). Oxidative coupling between **252** and 1,3-dienes provides nickelacycles **253**, which undergo selective β-carbon elimination via the C(sp^2)−C(sp^3) bond to provide Ni-allyls **254**. From here, C−C reductive elimination provides the products (e.g., **255a,b**), often in high diastereoselectivity. In the same report, cycloadditions between benzocyclobutenones and alkynes were demonstrated en route to naphthol derivatives (Scheme 58B). Note that these studies validate a complementary initiation mode to that employed by Dong in section 2.6.

Scheme 58. Oxidative Coupling−β-Carbon Eliminations Involving Benzocyclobutenones



3.5. Cyclobutane-based Processes

Hydro- and carbometalation can be used to trigger β-carbon elimination from alkylidenecyclobutanes in the same way as from alkylidenecyclopropanes (see section 3.2), and this area has been reviewed recently.[21] Representative recent examples are given below.

Aïssa and co-workers[202] have demonstrated intramolecular hydroacylations that generate eight-membered carbocycles (e.g., **257a,b**) via collapse of rhodacyclopentanones **256** (Scheme 59A). An example that generated a bicycle containing a fused pyridinium ring was also outlined. Processes employing alkylidene azetidines generate azocane ring systems (Scheme 59B).[202] Subsequent mechanistic studies indicated multiple C−C bond-cleavage events, via cyclopropyl-containing rhodacycles, for processes involving C2-substituted *Z*-configured alkylidenecyclobutanes.[203] Matsuda et al.[204] have shown that catalytically generated aryl-Rh(I) intermediates will add to polarized alkylidenecyclobutanes to provide spirocyclic ring systems (e.g., **263a,b**) (Scheme 59C). Here, conjugate addition provides **258**, which undergoes β-carbon elimination to generate **259**. [1,4]-Rhodium migration affords aryl-Rh intermediate **260**, which undergoes a further 1,4-addition to form Rh-enolate **261**. A further [1,4]-Rh migration generates aryl-Rh intermediate **262**, which undergoes 1,2-addition−elimination to provide the product. Examples involving other alkylidenecyclobutanes were also given. Subsequent studies directly generated intermediates related to **260** by transmetalation from arylboronic esters, which resulted in the same

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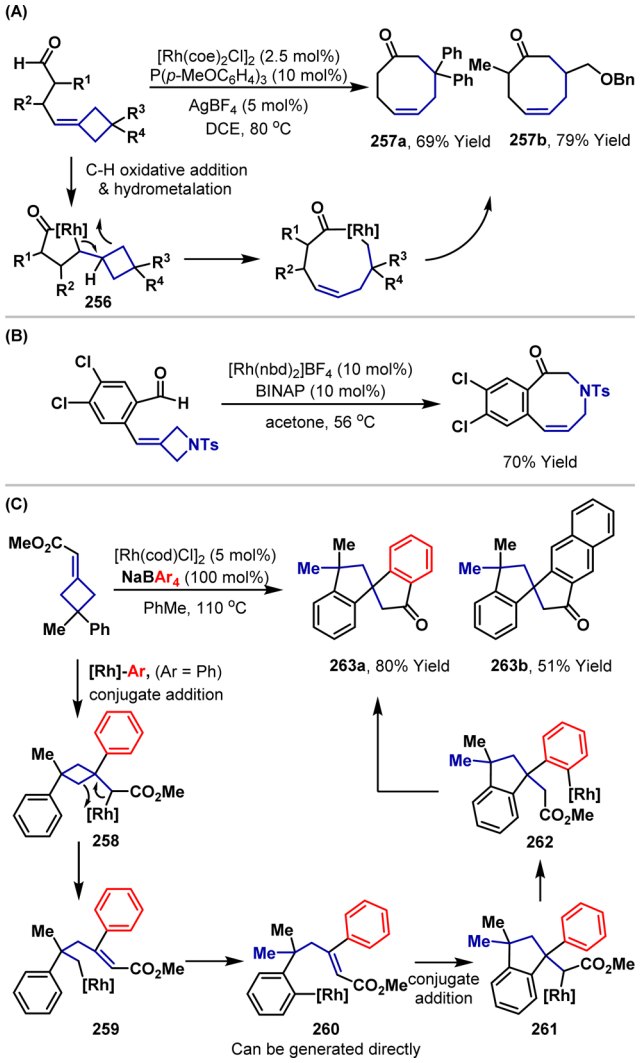
Scheme 59. β-Carbon Eliminations Triggered by Hydro- and Carbometalation of Alkylidenecyclobutanes



downstream pathway.[205] The process is a striking example of the mechanistic complexity on offer with such strategies.

4. CONCLUSIONS AND OUTLOOK

The processes outlined in this review encompass key recent C−C oxidative addition and β-carbon elimination-based methodologies that exploit strain embedded within small ring systems. Progress using both activation modes for reaction design has been rapid, driven in part by the opportunities for enantioselective and atom-economical assembly of complex carbon-based building blocks and ring systems. Although the number of substrate classes that are suitable for catalysis initiation is still relatively small, the overall diversity of recent processes is striking, especially in the context of cascade reactions. One particularly attractive application is the use of strain release to enable the synthesis of medium-sized ring systems.

Challenges going forward include the identification of catalyst systems and control strategies that are able to exploit a wider range of strained ring systems. For example, processes based on C−C activation of nonactivated cyclopropanes and cyclobutanes are still relatively rare yet evidently offer significant opportunities; here, a key issue is achieving regiocontrol for C−C cleavage. It is important to appreciate that the methodologies discussed here have a natural synergy with the synthetic accessibility of the small ring system used for reaction initiation. Consequently, going forward, the most powerful C−C cleavage processes should harness the most readily available substrate classes, which, in turn, should be accessible in an atom-economical manner. Ideally, new methodologies should also capitalize on either predictable enantioselective C−C cleavage of the small ring or transfer of easily installed stereochemistry from this unit to the product.

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Notes

The authors declare no competing financial interest.

Biographies

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Steven Stanton graduated from the University of St. Andrews in 2015 with an M.Chem. degree in chemistry with medicinal chemistry, completing his final year project in the laboratory of Professor Nicholas Westwood. During his undergraduate degree, he also spent a year on placement in the pharmaceutical industry with RedX Oncology in Liverpool. He began his Ph.D. studies in September 2015 under the supervision of John F. Bower, where he is developing new C−C activation-based methodologies.

John F. Bower obtained an M.Sci. in 2003 from the University of Bristol, where he remained to study for a Ph.D. (2007) under the guidance of Professor Timothy Gallagher. He then undertook postdoctoral appointments with Professor Michael Krische at the University of Texas at Austin (2007−2008) and Professor Timothy Donohoe at the University of Oxford (2008−2010). In 2010, he was awarded a Royal Society University Research Fellowship and commenced his independent career at the University of Bristol. His research has been recognized by a number of awards, including the 2013 Royal Society of Chemistry Harrison−Meldola Memorial Prize, the 2015 Royal Society of Chemistry Hickinbottom Award, and a 2016 Philip Leverhulme Prize.

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