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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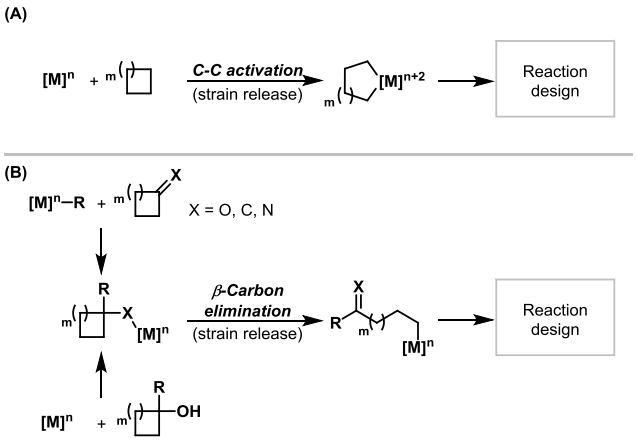
1. Introduction

Small (3- and 4-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 using undirected or directed approaches, with the latter often enhancing reaction rates and/or offering increased regiocon-

trol (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).

Scheme 1. C-C cleavage of small rings by (A) C-C activation and (B) β-carbon elimination.

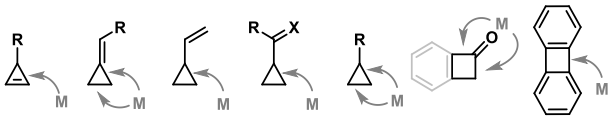


The purpose of this review is to highlight key methodologies involving strained ring systems that exploit these C-C single bond cleavage mechanisms. This area has developed rapidly in recent years and this review concentrates on key synthetic advances reported from mid-2009 to mid-2016; earlier developments involving strained[3-5] and non-strained 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.

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 reported the insertion of $PtCl_2$ into cyclopropane to generate a platinacyclobutane.[10] Cyclopropane-based ring systems have thus emerged as key initiating motifs in C-C activation methodologies (Figure 1). The introduction of 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.

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

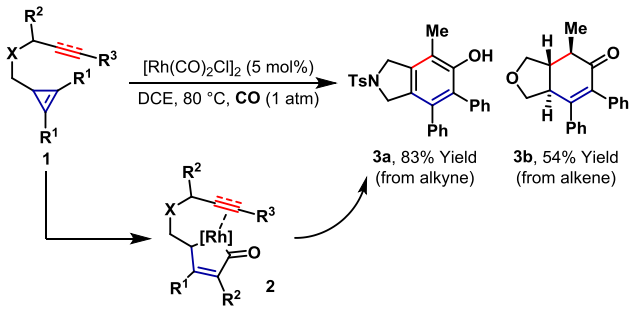


2.1 Cyclopropene-based processes

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 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).[17] 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 alkenes, high *trans*-diastereoselectivity was observed for the newly formed ring junction.

Scheme 2. Rh-catalyzed carbonylative (3+1+2) cycloadditions of cyclopropenes with alkynes and alkenes.

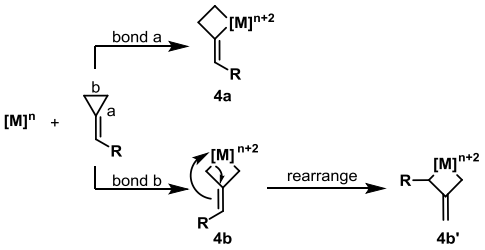


Wang and co-workers further exploited Rh-insertion into cyclopropenes to effect rearrangement of systems possessing adjacent cyclopropylsilyl ethers, which provided cyclohexenones.[18] Further developments in this area have been limited. However, although outside of the scope of this review, C-C cleavage 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

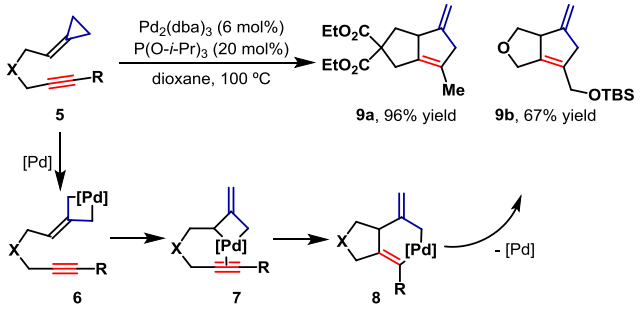
Alkylidenecyclopropanes (ACPs), although less strained than cyclopropenes (approximate strain energies of 39 vs 55 kcal/mol),[13] are still highly reactive to C-C oxidative addition.[15,21-23] Here, metal insertion can occur into proximal bond a or distal bond b, with examples of both types of process reported recently (Scheme 3). The resulting *exo*-methylene metallacyclobutanes are either captured directly or, for **4b**, allowed to rearrange prior to engagement with a tethered π-unsaturated component. Building on Noyori's studies in the 1970's with Ni-catalysts, which tend to insert into bond a,[24,25] cycloadditions catalyzed by a range of transition metals (Ni, Ru, Pd, Rh) have emerged, and this area has been reviewed.[26,27]

Scheme 3. Transition metal insertion into alkylidenecyclopropanes.



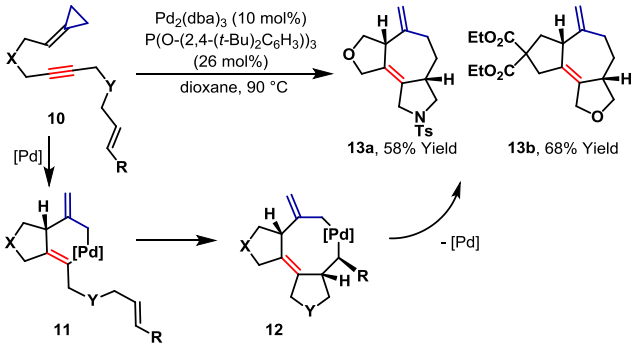
For subsequent discussion, it is pertinent to summarize a 2003 report from the Mascareñas group, who developed palladium-catalyzed (3+2) cycloadditions of ACPs with pendant alkynes to generate bicyclic systems (e.g. **9a**/**b**) (Scheme 4).[28] Computational studies support initial insertion of the palladium complex into the distal C-C bond of **5**, followed by isomerization (to **7**) and coordination to the tethered alkyne.[29] Carbometallation and reductive elimination then affords the products in good to excellent yields. Subsequent developments from the Mascareñas group included substantial rate enhancements by using bulkier phosphite ligands,[30] the identification of complementary Ru-based systems,[31] and processes where the alkyne is replaced by an alkene.[32]

Scheme 4. Pd-catalyzed cyclizations of alkylidenecyclopropanes with tethered alkynes.



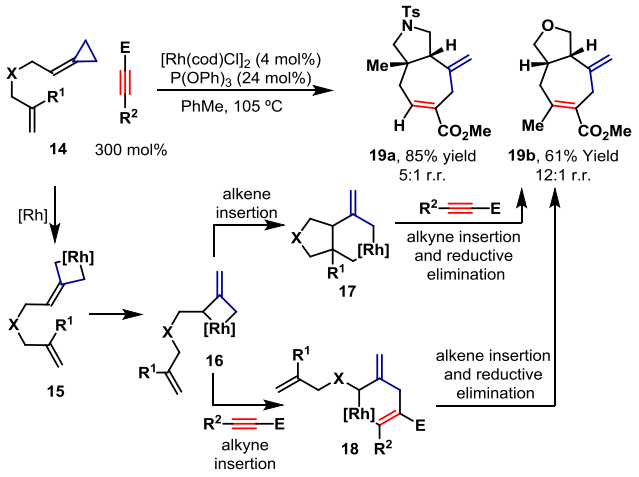
The process in Scheme 4 involves three distinct organometallic intermediates, each of which could serve as the basis for further reaction development. Indeed, trapping of **7** with other "inserting" groups was quickly realized to provide flexible access to other ring systems. For example, replacement 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, the Mascareñas group achieved this by including an additional tethered alkyne/alkene (Scheme 5).[35] Here, formation 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 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.[36] 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]

Scheme 5. Pd-catalyzed (3+2+2) cycloadditions of alkylidenecyclopropanes.

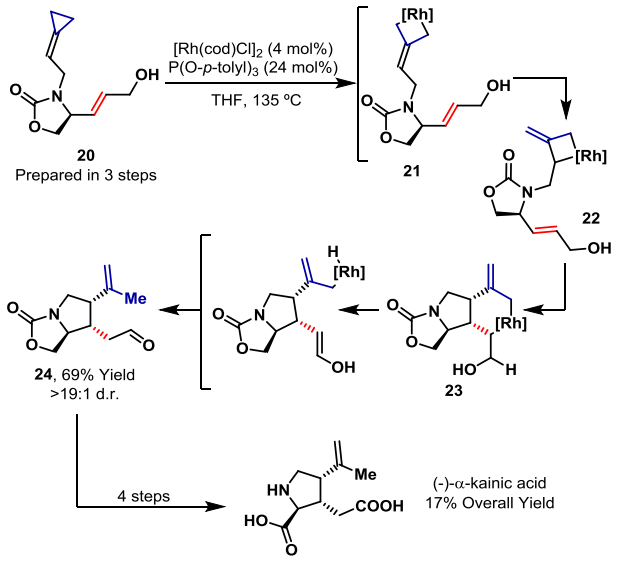


The Mascareñas Rh-catalyzed (3+2+2) process[36] was pre-dated by a report from the Evans group in 2008, which disclosed powerful partially intermolecular (3+2+2) cycloadditions using alkylidenecyclopropanes (Scheme 6).[38] Here, exposure of substrates **14** and electron deficient alkynes to a phosphite-ligated neutral Rh(I)-system generated regioisomeric bicyclic products (e.g. **19a**/**b**) with between 4:1 and >19:1 regioselectivity. 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 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, which provided higher reactions rates and regioselectivities vs the process in Scheme 6.[40]

Scheme 6. Partially intermolecular Rh-catalyzed (3+2+2) cycloadditions of alkylidenecyclopropanes, alkenes and polarized alkynes.



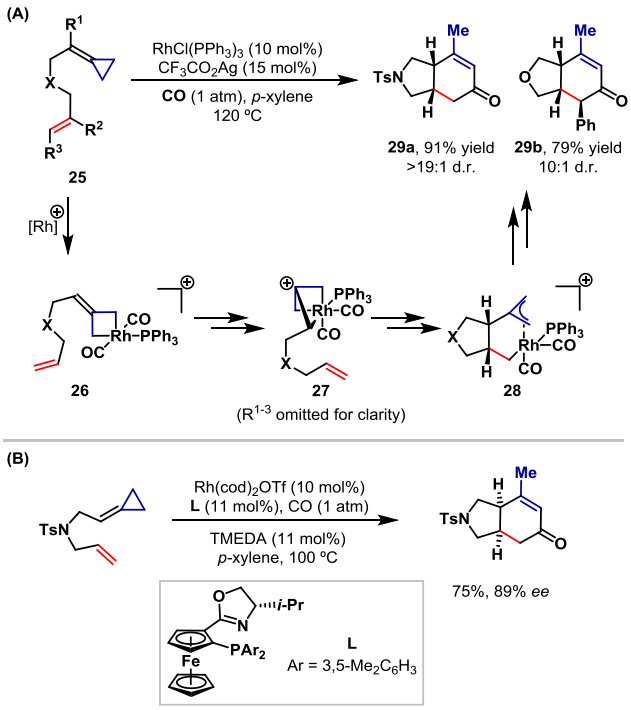
Scheme 7. Rh-catalyzed ene-cycloisomerization en route to (-)-α-kainic acid.



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 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 d.r.. The proposed mechanism is supported by deuterium labelling studies on a related substrate.

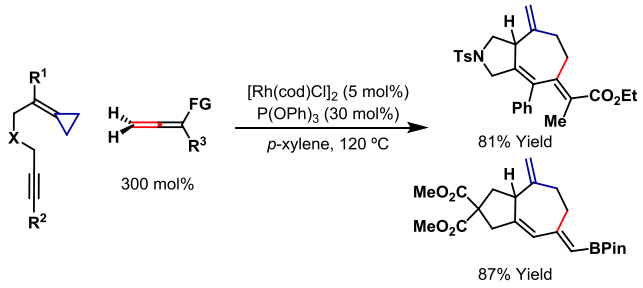
More recent studies from the Evans group have focused on gaining an in depth understanding of the isomerization process that occurs after oxidative addition of Rh(I) into alkylidenecyclopropanes. Using an in situ generated cationic Rh(I)-system modified with PPh_3, substrates **25** engage in (3+1+2) cycloadditions with CO to generate cyclohexenones (e.g. **29a**/**b**) (Scheme 8A).[42] Preliminary results using a chiral P,N-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 complex **27** have previously been ruled out as intermediates in alkylidenecyclopropane (3+2) cycloadditions (vide infra).[24,25] Later, Chung and Kim reported a process related to that shown in Scheme 8A, where the alkene was replaced by an alkyne to generate phenols.[43]

Scheme 8. Rh-catalyzed carbonylative (3+2+1) cycloadditions and a computationally supported mechanism.

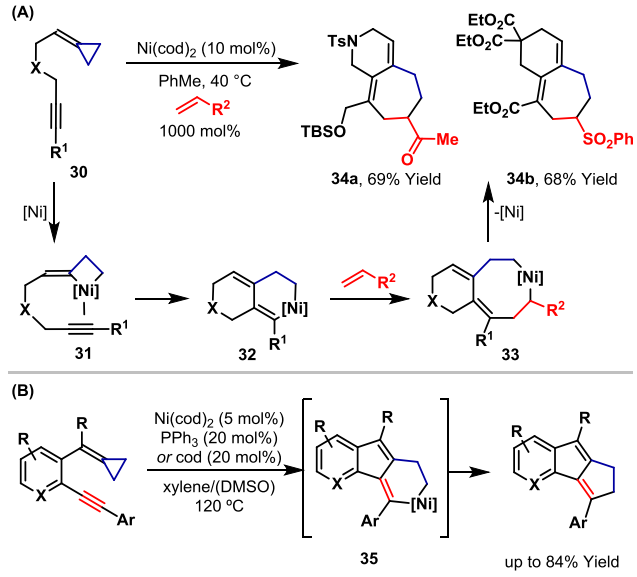


Subsequent studies succeeded in isolating and characterizing neutral rhodium complexes related to **27**; these underwent insertion of alkynes and CO and were also shown to be catalytically competent.[44] By employing these isolable metallacycles as a starting point, (3+2+2) cycloadditions involving exogenous allenes were demonstrated and this led to a catalytic protocol (Scheme 9).[45] The approach enables the preparation of challenging seven membered rings bearing allene derived tri- and tetra-substituted exocyclic olefins; the geometry of this unit is controlled by preferential *syn*-carbometallation of the less hindered face of the terminal allene π-bond. It was also shown that the approach can be used for the construction of 6,7-bicyclic systems by increasing the alkyne tether length.

Scheme 9. Rh-catalyzed (3+2+2) cycloadditions of alkylidenecyclopropanes, alkynes and allenes.



Scheme 10. (A) Ni-catalyzed (3+2+2) cycloadditions of alkylidenecyclopropanes, alkynes and alkenes. (B) Ni-catalyzed (3+2) cycloadditions of alkylidenecyclopropanes and alkynes.

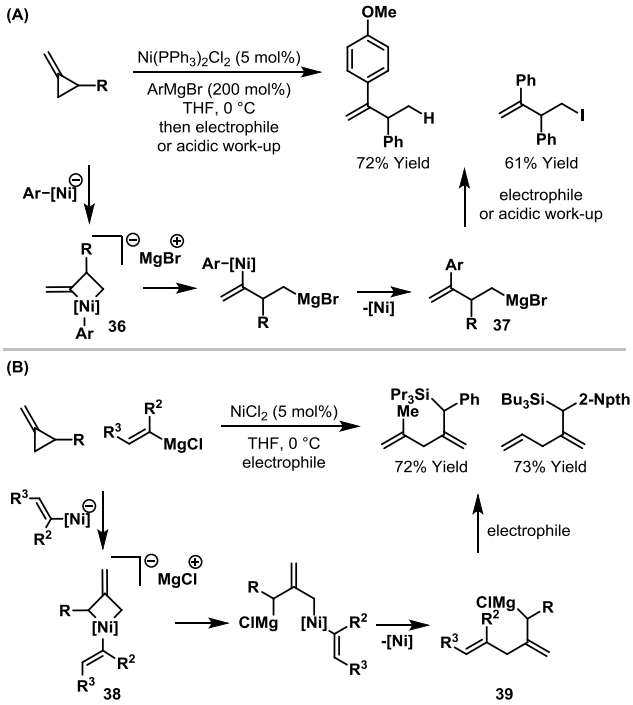


Although ligand dependent, it has been known since the 1970's that Ni-catalyzed cycloadditions of alkylidenecyclopropanes often proceed via direct insertion into the proximal C-C bond,[24,25] rather than into the distal C-C bond. This contrasts the Pd- and Rh-catalyzed processes discussed so far and enables access to different ring systems from the same precursors. The Mascareñas group exploited this observation to develop cycloadditions of precursors **30** which provided 6,7-bicyclic systems (e.g. **34a**/**b**) (Scheme 10A; cf. Scheme 6).[46] 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. **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 5-ring products. Computational studies were used to support the proposed mechanism and these 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 adapted this initiation mode to provide benzofused ring systems, by promoting reductive elimination from nickelacyclohexene intermediates **35** (Scheme 10B).[48]

In addition to the cycloaddition processes discussed so far, intermolecular couplings of methylenecyclopropanes have been developed. Kambe, Terao and co-workers showed that Ni-catalyzed multi-component coupling of methylenecyclopropanes with aryl or vinyl Grignard reagents generates α-substituted styrenes (Scheme 11A) or skipped dienes (Scheme 11B).[49] The proposed mechanism for both processes involves in situ generation of an anionic organo-Ni(0) species which either inserts into the proximal or distal methylenecyclopropane C-C bond to generate nickelacycles **36** and **38**. These undergo ring opening and C-C reductive elimination to release new Grignard reagents **37** and **39**, which are either quenched on work-up or in situ (alkyl halides/R_3SiCl). The proposed mechanisms were supported by deuterium labeling studies.

Scheme 11. Ni-catalyzed multicomponent cross-couplings of methylenecyclopropanes.

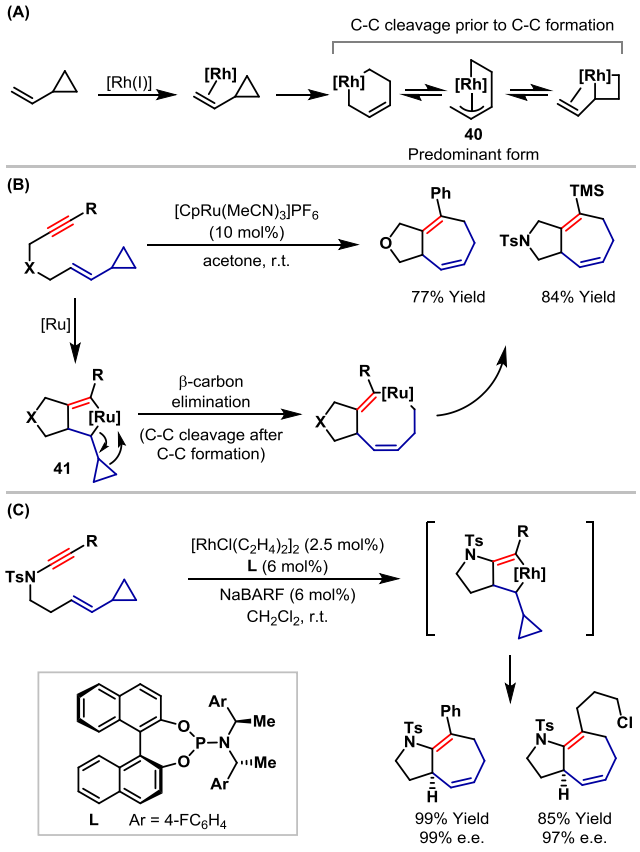


2.3 Vinylcyclopropane-based processes

The 3-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 Wender's seminal studies,[50] where, under Rh-catalyzed conditions, vinylcyclopropanes (VCPs) were established as 5-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 5-carbons of the vinylcyclopropane unit or the 3-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

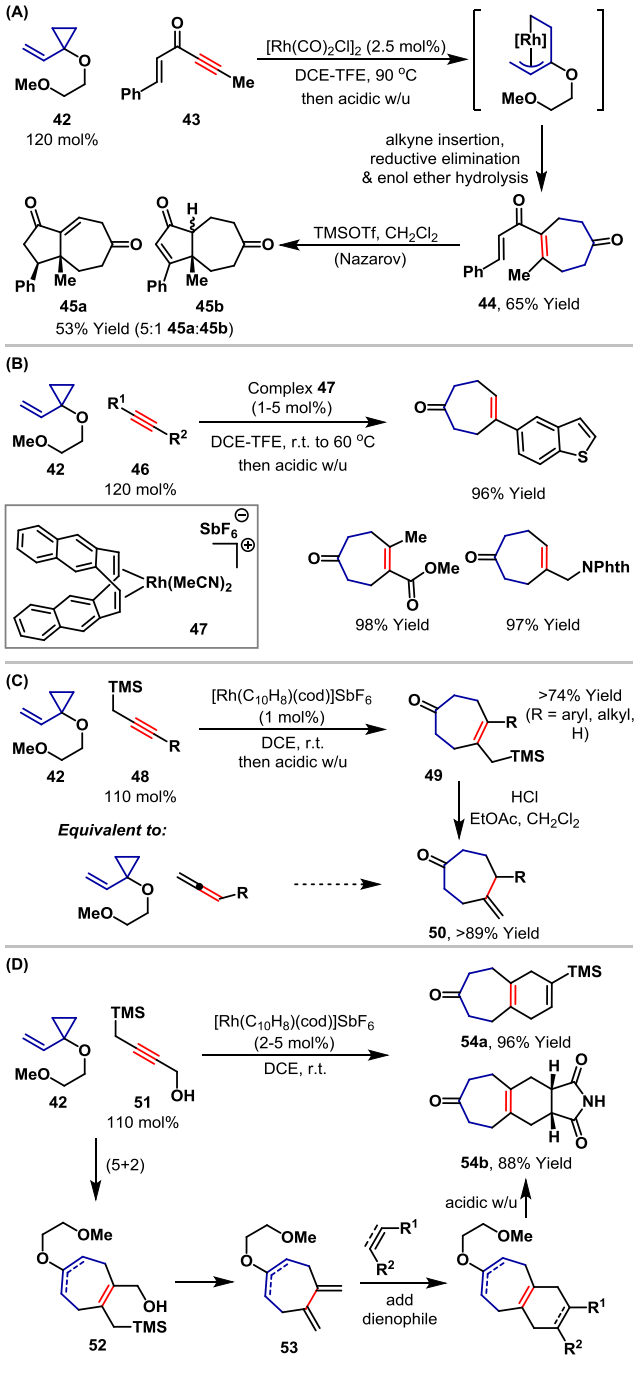
(5+2) processes reported by Trost and co-workers likely proceed via a distinct mechanism involving oxidative coupling (to **41**) in advance of β-carbon elimination and C-C reductive elimination (Scheme 12B).[55,56] Interestingly, computational studies support a similar scenario for enantioselective Rh-catalyzed intramolecular (5+2) cycloadditions of ynamides and VCPS developed recently by Anderson and co-workers (Scheme 12C); in this study elegant catalyst-controlled diastereoselective processes were also outlined.[57]

Scheme 12. (A) Oxidative addition of Rh(I)-catalysts to vinylcyclopropanes and mechanistically distinct (B) ruthenium- and (C) rhodium-catalyzed processes.



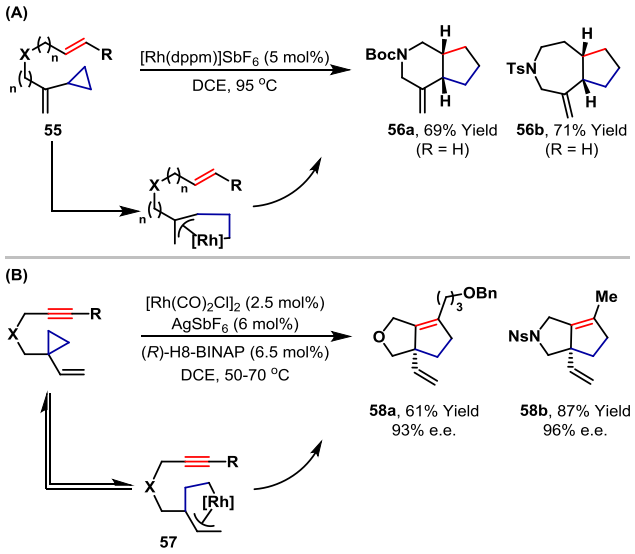
The Wender laboratory has extended the range of processes where vinylcyclopropanes are used as 5-carbon components in cycloadditions. Alkoxy-substituted vinylcyclopropanes such as **42** are especially effective in intermolecular processes. Indeed, previous studies demonstrated that **42** participates 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 subject of a computational study.[61] More recently, it was shown that Rh-catalyzed cycloaddition of **42** with enynone **43** generates 7-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 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 rationales 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 intermediates **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**.

Scheme 13. Intermolecular (5+2) cycloadditions of vinylcyclopropanes with alkynes.



The Yu laboratory 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 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-unsaturated, 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 e.e. using a cationic Rh-system modified with (*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]

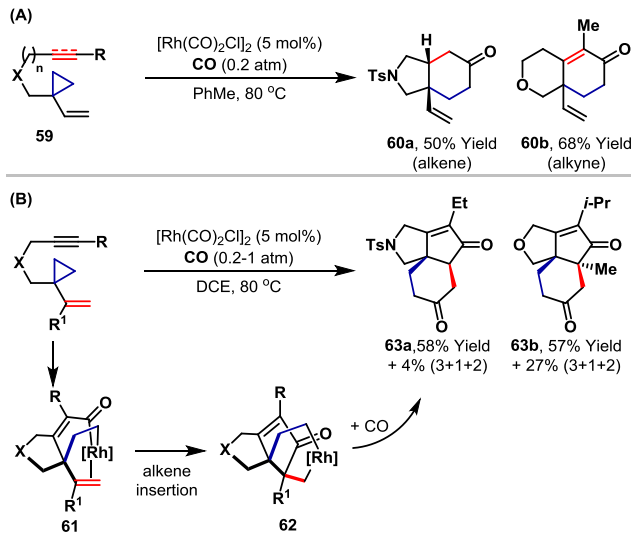
Scheme 14. Intramolecular (3+2) cycloadditions of vinylcyclopropanes with alkenes or alkynes.



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**)

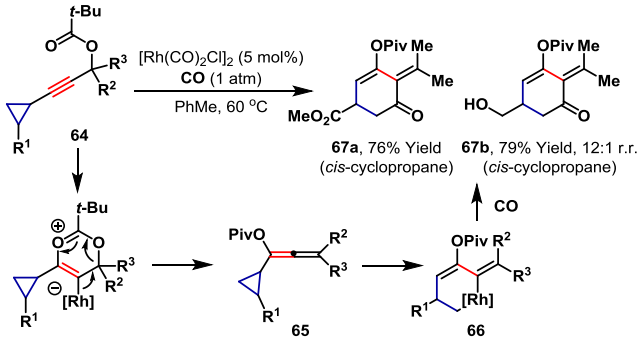
ring systems (Scheme 15A).[73] Presumably carbonylation occurs after the π-unsaturate has inserted in the initially generated rhodacycle. Indeed, subsequent studies involving internal alkynes provide angularly fused tricyclic ring systems (e.g. **63a**/**b**) (Scheme 15B).[74] In essence, these processes 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**. This 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. The Yu group 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]

Scheme 15. Higher order carbonylative cycloadditions of vinylcyclopropanes.

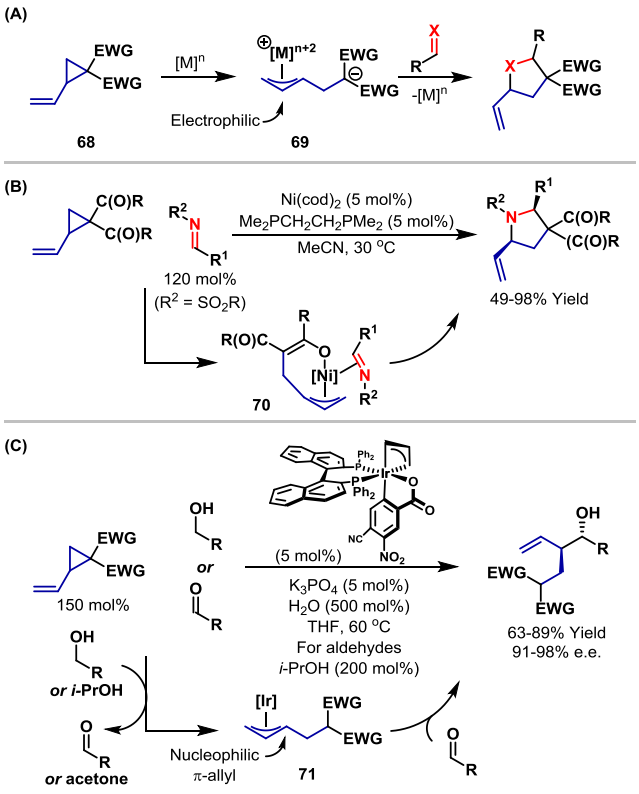


Cyclopropanes with other classes of adjacent C-based π-unsaturation are also active in Rh-catalyzed cycloadditions. An interesting example was reported by the Tang group in 2011, involving generation of allenylcyclopropanes in situ (Scheme 16).[77] Here, Rh-catalyzed rearrangement of propargylic pivalates **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, 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 using preformed allenylcyclopropanes and this provided a formal synthesis of (-)-galanthamine.[79]

Scheme 16. In situ generation and carbonylation of allenyl cyclopropanes.



Scheme 17. Metal catalyzed cycloadditions and C-C bond formations using "donor-acceptor" vinylcyclopropanes.



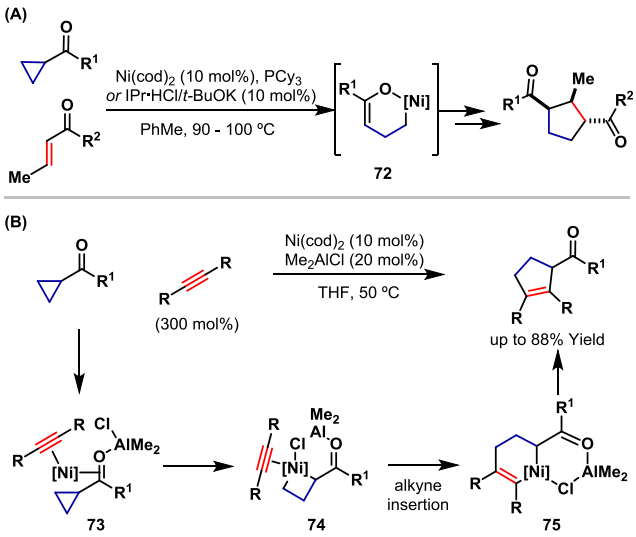
Another key area of catalysis based on oxidative addition of transition metals to vinylcyclopropanes involves "donor-acceptor" systems **68**, which are set-up for S_N2 like oxidative addition (Scheme 17A). This generates simultaneously an electrophilic π-allyl and a stabilized carbanion (**69**), thus 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 co-workers,[80,81] and Fe-catalyzed homo-conjugate additions of Grignard reagents, as reported by Fürstner and Sherry.[82] Plietker and co-workers subsequently demonstrated Fe-catalyzed cycloadditions involving electron deficient alkenes.[83] Matsubara, Kurahashi and Tombe developed Ni-catalyzed cycloadditions with imines to provide vinyl pyrrolidines (Scheme 17B).[84] 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 developed Ni-catalyzed reductive couplings with alkynes to provide skipped dienes based on the same activation mode.[85] Johnson, Krische and co-workers reported polarity inversion of "donor-acceptor" cyclopropanes under Ir-catalyzed transfer hydrogenative conditions (Scheme 17C).[86] The process converts the vinylcyclopropane precursor into a neutral nucleophilic metal allyl (**71**) which can engage (in situ generated) aldehydes 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 and co-workers reported the generation of nucleophilic Pd-allyls using $ZnEt_2$ as reductant, and showed that these react smoothly with carbon dioxide.[88]

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. The groups of Montgomery and Ogoshi have demonstrated that cyclopropyl ketones or imines can engage alkenes to provide cyclopentanes in the presence of Ni-catalysts.[89-93] For cyclopropyl ketone-based pro-

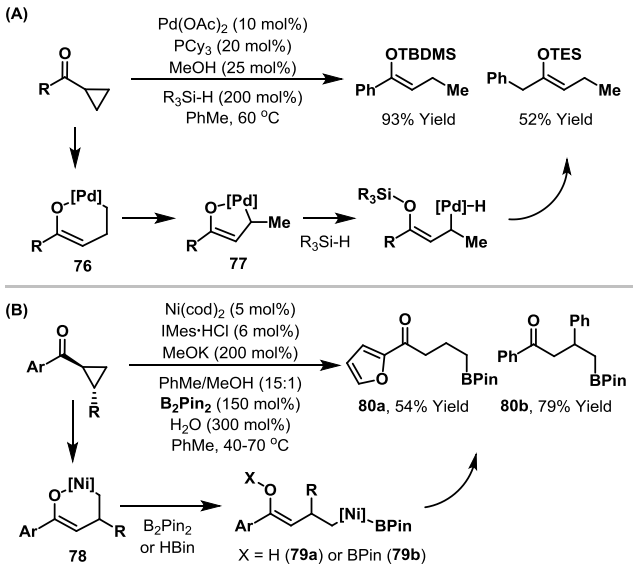
cesses, 6-ring oxa-nickelacycles **72** were identified as key intermediates (Scheme 18A).[92,93] However, replacement of the alkene with alkynes did not facilitate related cyclopentene formations. Ogoshi and co-workers have addressed this issue by developing a method which employs Me_2AlCl as a Lewis acidic additive (Scheme 18B).[93] 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 oxa-nickelacyclohexene (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.

Scheme 18. (A) Ni-catalyzed (3+2) cycloadditions of cyclopropyl ketones with alkenes. (B) Ni-catalyzed (3+2) cycloadditions of cyclopropyl ketones with alkynes.



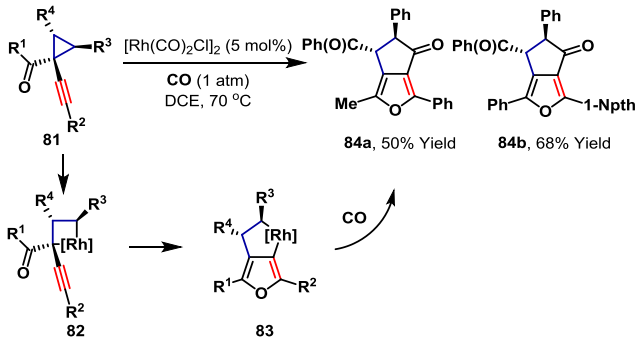
The Oshima group has also developed metal-catalyzed hydrometallations of cyclopropyl ketones. Under Pd-catalyzed conditions, various trialkylsilanes combine with cyclopropyl ketones to provide silyl enol ethers with high (*Z*)-selectivity (Scheme 19A).[94] The proposed mechanism invokes oxidative addition by an in situ generated Pd(0) complex to provide palladacycle **76**. This isomerizes to 5-membered palladacycle **77** by a β-hydride elimination-hydrometallation sequence. Transmetallation with the silane is followed by C-H reductive elimination to deliver the product. The proposed mechanism is supported by deuterium labelling 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 work-up, provide γ-borylated ketones (e.g. **80a**/**b**). The process was also demonstrated on 1,1- and 1,2-disubstituted cyclopropanes.

Scheme 19. (A) Pd-catalyzed hydrosilylation and (B) Ni-catalyzed formal hydroborylation of cyclopropyl ketones.



Other metals have been shown to insert in to specific subclasses of cyclopropyl ketone. Zhang and co-workers effected carbonylative isomerization of alkynyl systems **81** to bicyclic furans (e.g. **84a/b**) (Scheme 20).[96] The proposed mechanism involves C-C oxidative addition prior to rearrangement of **82** to 5-membered rhodacycle **83**. Insertion of CO and reductive elimination then provides the products.

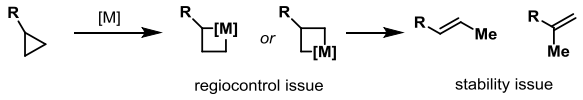
Scheme 20. Carbonylative rearrangement of alkynyl cyclopropyl ketones.



2.5 Processes based on less activated cyclopropanes

Metal-catalyzed activation of "non-activated" 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 non-activated cyclopropanes possess three electronically similar C-C bonds (Scheme 21).

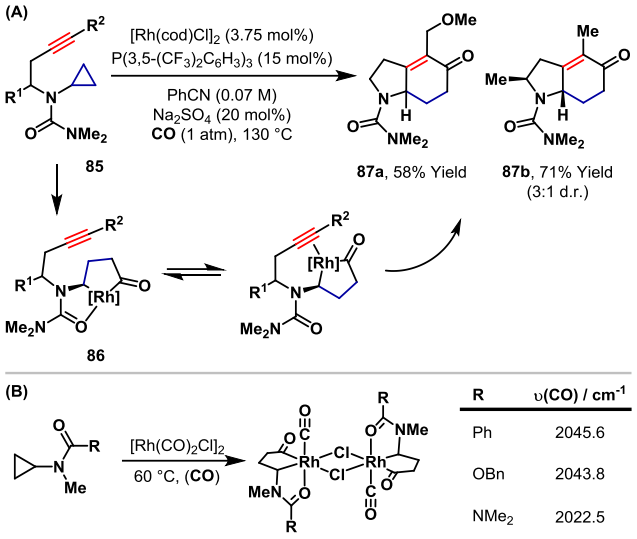
Scheme 21. Metal-catalyzed activation of non-activated cyclopropanes.



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

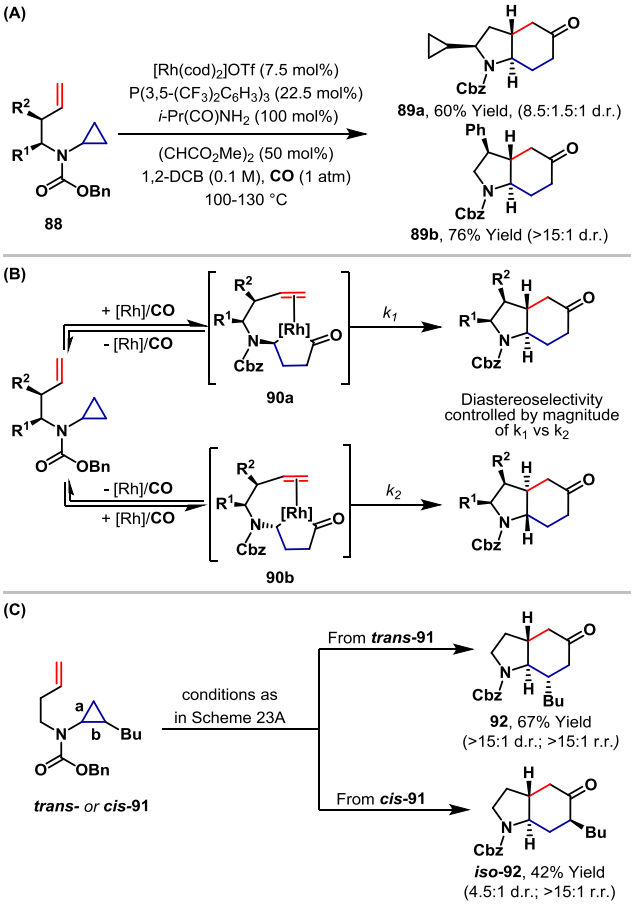
There have been significant recent developments in the area of rhodacyclopentanone based catalysis,[100] which are discussed within the next two sections of this review. In 2013, the Bower group reported N-protecting group directed generation of rhodacyclopentanones as the basis for a (3+1+2) cycloaddition strategy (Scheme 22A).[101] 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 using weaker carbamate directing groups (e.g. Cbz) (Scheme 23A).[103] 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 the 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. Retro-carbonylation from **90a**/**b** requires a vacant coordination site on the Rh-center. As 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 of 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 more hindered bond b to provide regioisomeric adduct ***iso*-92**.

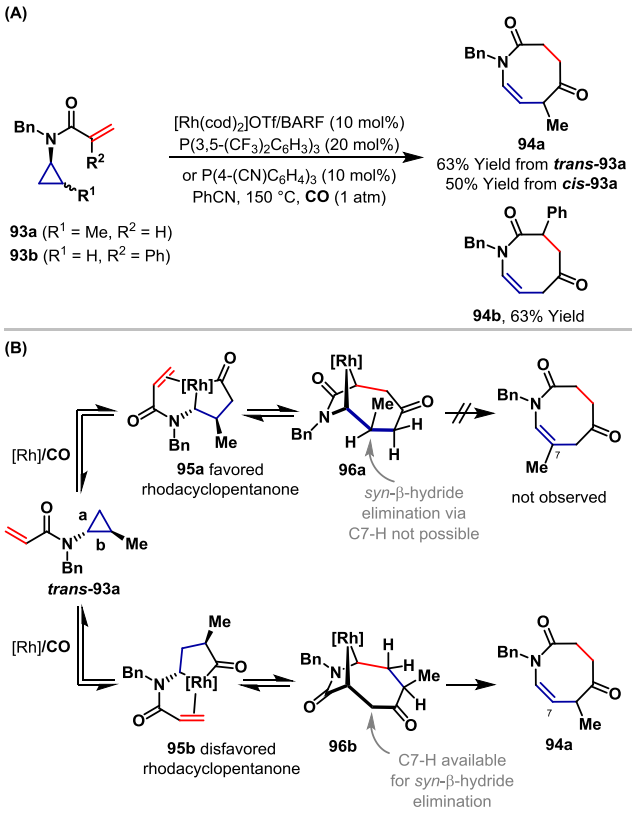
Scheme 23. Protecting group directed carbonylative (3+1+2) cycloadditions of aminocyclopropanes and alkenes.



The Bower group extended their approach to carbonylative cycloadditions of N-cyclopropyl acrylamides **93** (Scheme 24A).[104] 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 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 8-membered ring that would result.

Scheme 24. Protecting group directed carbonylative (7+1) cycloadditions of aminocyclopropanes and alkenes.

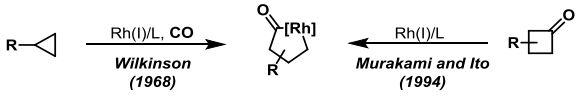


The processes outlined above represent the major developments in this area although there have been other sporadic reports of C-C activation involving relatively non-activated cyclopropanes. For example, René and co-workers have shown that Pd(0)-systems will insert into spirocyclopropanes to allow ring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

2.6 Cyclobutanone and benzocyclobutenone-based processes

Seminal studies by Murakami and Ito demonstrated non-directed insertion of Rh(I)-catalysts into the C-C bond of ketones, including cyclobutanones.[106] Subsequently, catalytic processes involving cyclobutanones were developed, with the approach providing an alternative entry to rhodacyclopentanones vs cyclopropane rhoda-carbonylation (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]

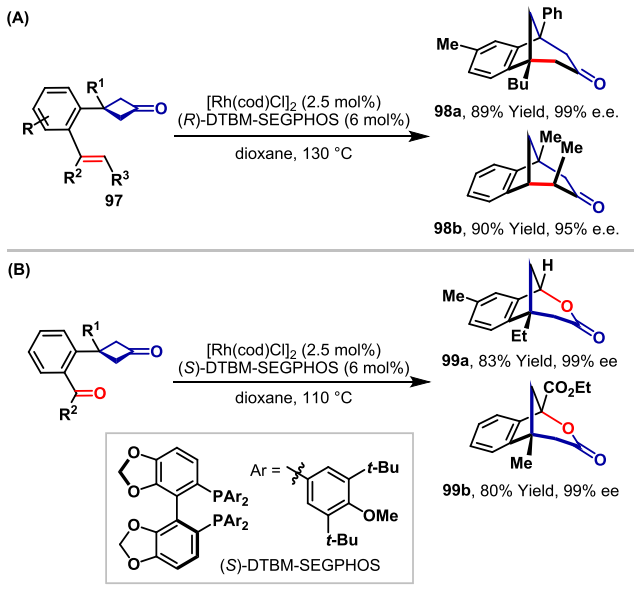
Scheme 25. Rhodacyclopentanones via C-C bond activation.



Building upon earlier studies by Murakami,[108] Cramer and co-workers succeeded in rendering cyclobutanone π-insertion processes enantioselective (Scheme 26A).[109-110] Here, styrenyl systems **97** underwent enantioselective C-C bond activation, using a Rh(I)-system modified with 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-unsaturate can also be exploited. Indeed, Cramer and co-workers later showed that insertion of carbonyls provides lactones

(e.g. **99a/b**) in high enantioselectivity (Scheme 26B).[111] Interestingly, the process tolerates aldehydes, even though these are prone to decarbonylation under Rh-catalyzed conditions.

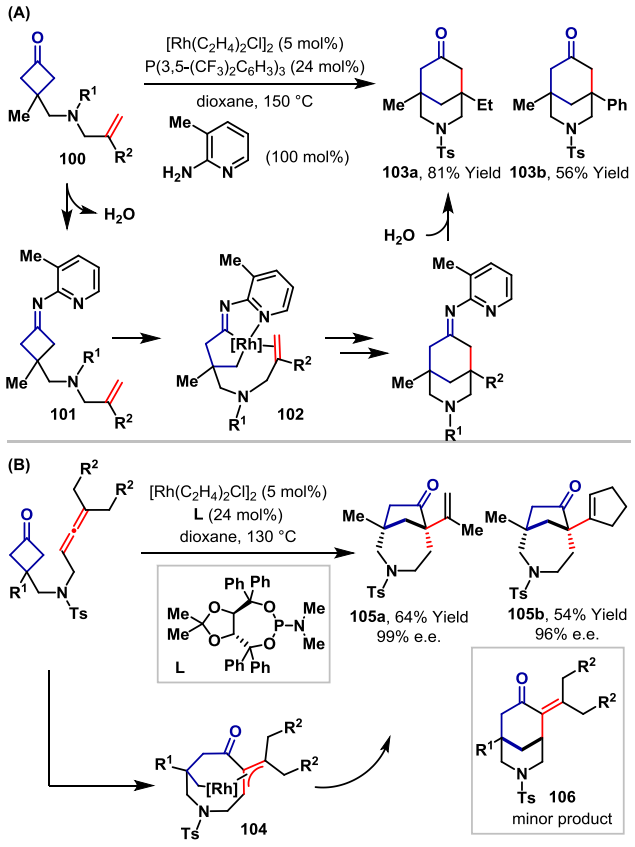
Scheme 26. Enantioselective π-insertion into cyclobutanones.



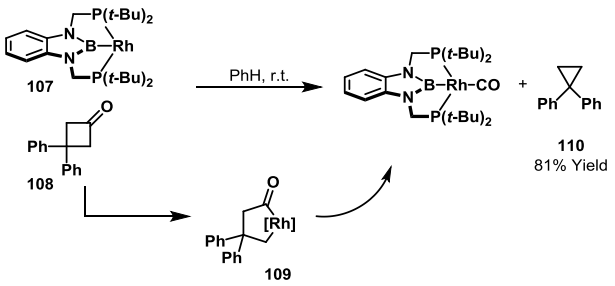
Decarbonylation at the stage of the rhodacyclopentanone is often a major inefficiency associated with the cyclobutanone activation processes outlined here. To address this, Dong and co-workers adapted Jun's pyridyl directed C-C activation strategy to cyclobutanone π-insertion processes (Scheme 27A).[112,113] Exposure of cyclobutanones **100** to 2-amino-3-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 6-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, Nozaki, Yamashita and co-workers have demonstrated room temperature activation of cyclobutanones (and benzocyclobutenones), using PBP-pincer complex **107** (Scheme 28).[115] This inserted smoothly into cyclobutanone **108** 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.

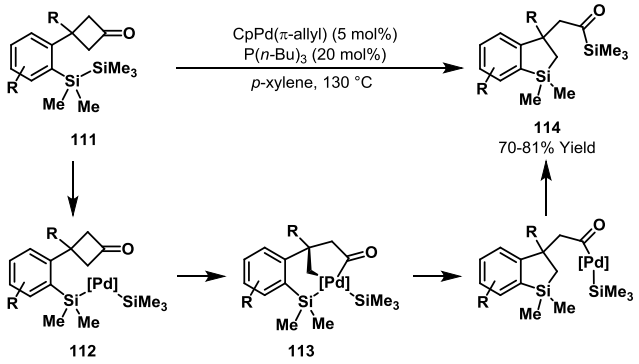
Scheme 27. (A) Temporary directing group assisted π-insertion into cyclobutanones; (B) non-directed allene insertion in cyclobutanones.



Scheme 28. Room temperature C-C activation of a cyclobutanone.

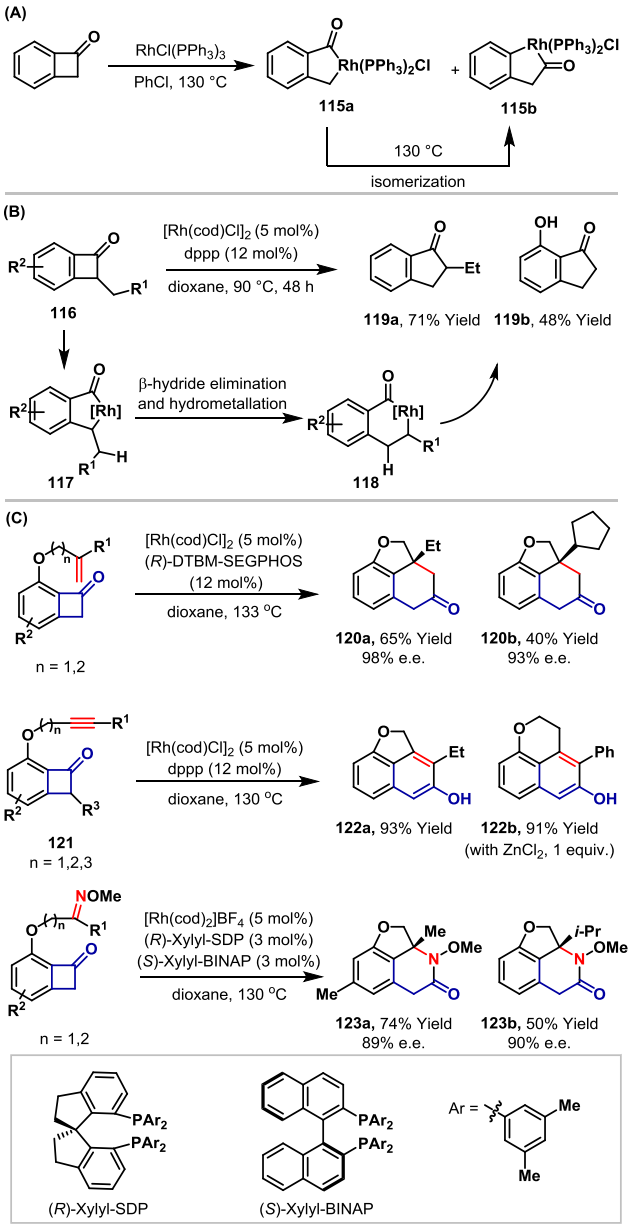


Scheme 29. Pd-catalyzed cyclobutanone C-C bond activation by initial insertion into a proximal Si-Si bond.



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 have shown that activation of cyclobutanones **111** is possible under the conditions of Pd-catalysis (Scheme 29).[116] In the 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**.

Scheme 30. Rhodaindanones and associated catalytic processes.

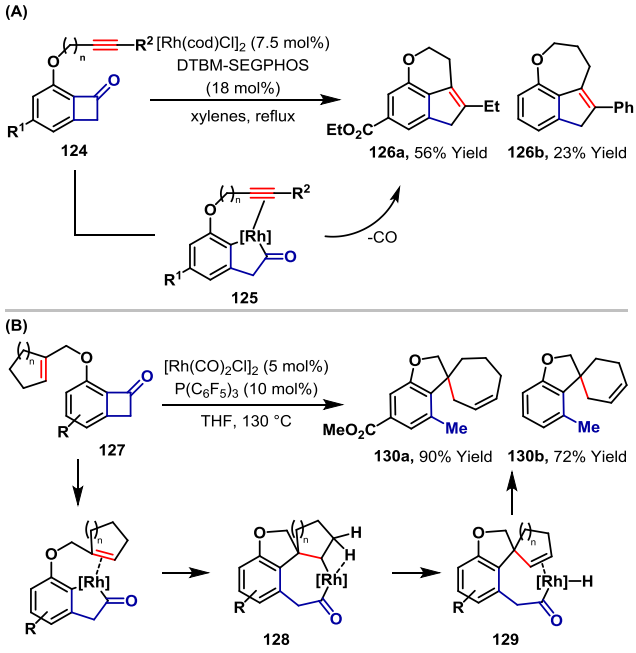


In 1992, Liebeskind and co-workers showed that Wilkinson's catalyst can insert into the C(sp^3)-acyl bond of benzocyclobutenone to provide rhodaindanone **115a** (Scheme 30A).[117] This underwent thermal isomerization to thermodynamically favored regioisomer **115b**. Recent computational studies suggest that this occurs via retrocarbonylation-recarbonylation from **115a**.[118] The Dong laboratory have 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 the rhodaindanone **117**, hydrometallation and C-C reductive elimination from **118**. Other processes require rearrangement of the initially formed 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**) in 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 insertions of oximes generating complex lactam products (e.g. **123a/b**) in high enantioselectivity.[124] Here, a double chiral ligand system was employed, with (*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 have also found that related decarbonylative processes can be achieved. For example, using DTBM-SEGPHOS as ligand, cyclization of substrates **124** provides 6- and 7-ring cyclic ethers (e.g. **126a/b**) fused to an indene ring (Scheme 31A).[123] CO loss 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]

Scheme 31. Decarbonylative cycloadditions of benzocyclobutenones.



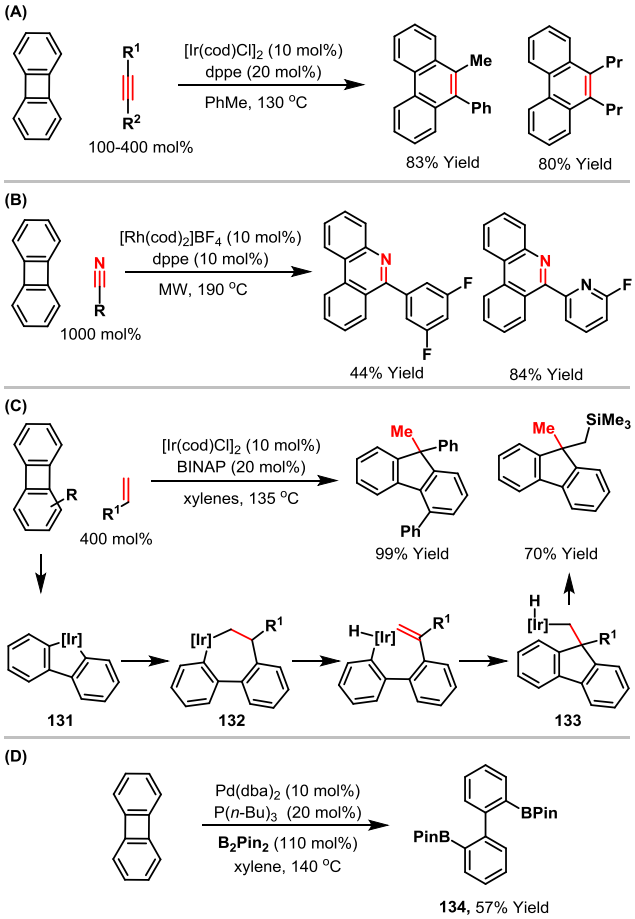
The above discussion summarizes the major recent developments in C-C activation of 4-membered rings, with cyclobutanone-based systems underpinning all the methodologies. Thus internal activation of the cyclobutane ring is required, even though cyclobutane itself embodies only marginally less strained 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 the Matsuda laboratory, concerning directed activation of (2-pyridylmethylene)cyclobutenes are of note.[127,128] 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 4-membered ring systems. As

early as 1964, it was shown that exposure of biphenylene to $Cr(CO)_6$ generated small quantities of fluorenone.[130] Subsequent historical developments have been reviewed,[131] with the focus here on a selection of recent methodologies only.

Scheme 32. Selected recent methodologies involving C-C activation of biphenylenes.



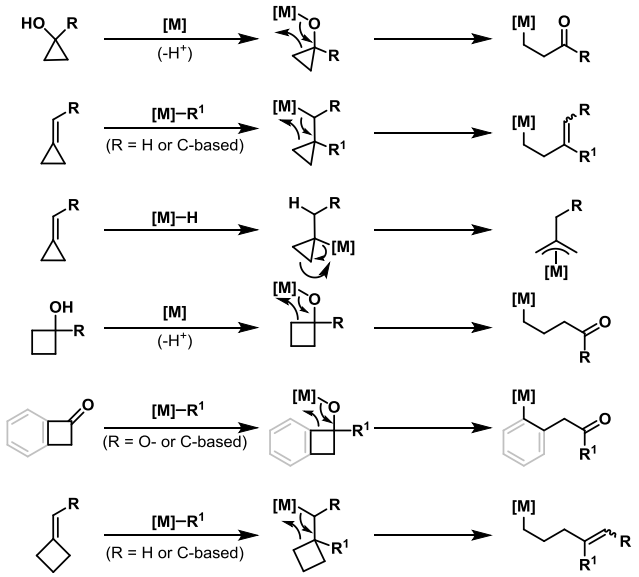
From a synthetic viewpoint, perhaps the most attractive processes are those which involve C-C activation triggered insertion of C-based units into biphenylenes. Roithová, Kotora and co-workers have demonstrated efficient Ir(I)-catalyzed insertion of disubstituted alkynes to provide highly conjugated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

3. β-Carbon elimination-based methodologies

The methodologies discussed so far all involve C-C oxidative addition and, as such, can be termed as "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.

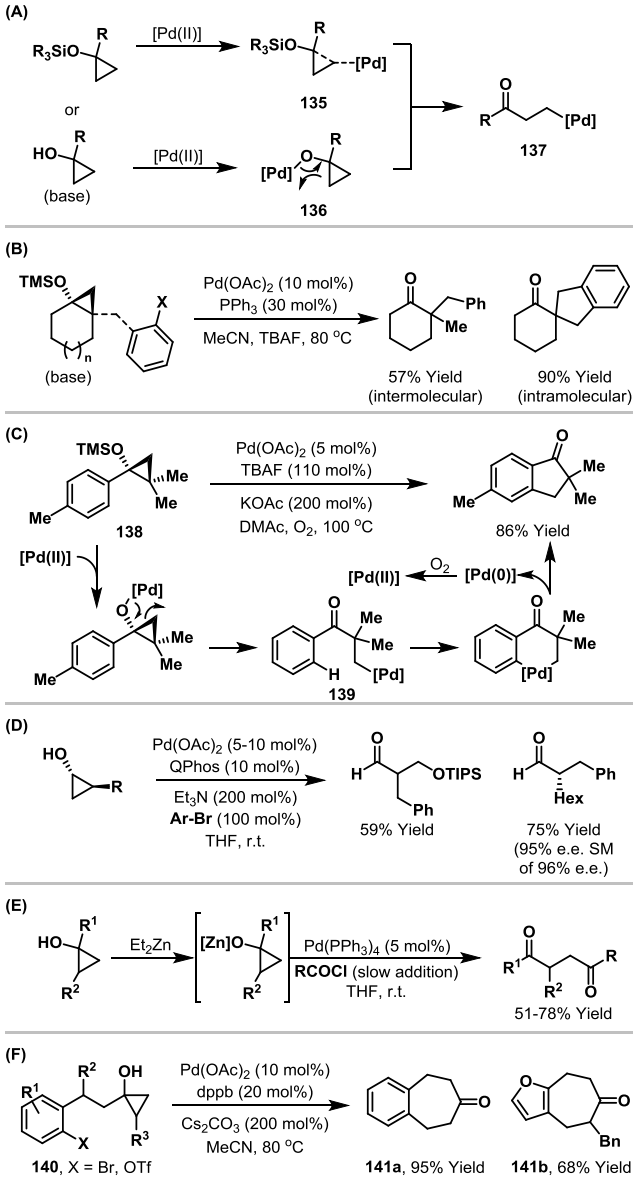


3.1 Cyclopropanol-based processes

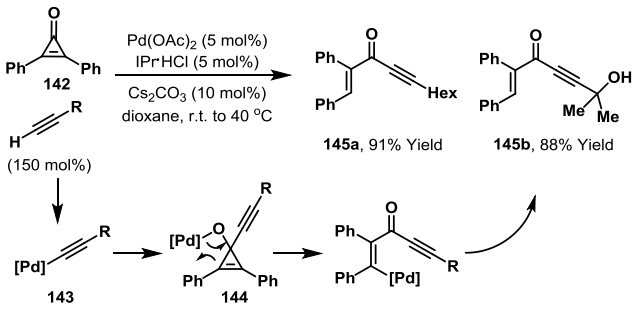
Cyclopropanol silyl ethers function as homo-enolate equivalents as demonstrated by Kuwajima and Nakamura in 1977.[138] When used in Pd-catalysis, Nakamura's studies suggest C-C cleavage by way of "corner attack" onto the Pd(II)-center (**135**) (Scheme 34A).[139] Later, Cha demonstrated that unprotected cyclopropanols could also be engaged in C-C bond activation.[140] Here, it was proposed that β-carbon elimination from alkoxy intermediates **136** generates alkyl-Pd(II) intermediates **137**. Orellana and Rosa demonstrated inter- and intra-molecular processes involving cyclopropanol silyl ethers that are triggered by aryl-Pd(II) intermediates generated from aryl halides (Scheme 34B).[141] Note that 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 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. Walsh and Cheng addressed this issue by reporting a QPhos enabled system that was effective at room temperature with aryl bromides (Scheme 34D).[143] 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 showed that acid chlorides are competent partners for coupling with zinc cyclopropanoxides generated in situ (Scheme 34E).[144] The approach is notable in providing direct access to 1,4-diketones. For cases involving non-symmetrical 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 using alkynyl bromides as the electrophile to provide β-alkynylated ketones.[146] Intramolecular variants are particularly powerful for the construction of carbocycles; Cha and co-workers showcased this in the construction of challenging 7-ring systems (e.g. **141a**/**b**), where initiation occurs by oxidative addition into pendant aryl or alkenyl (pseudo)halides of **140** (Scheme 34F).[147] Dai and co-workers have developed copper-catalyzed conditions that enable trifluoromethylation, thiotrifluoromethylation and amination of cyclopropanols.[148,149] 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 demonstrated efficient Pd-catalyzed conversion of cyclopropenone **142** and alkynes to yne-enone products (e.g. **145a**/**b**) (Scheme 35).[151] The reaction is believed to involve 1,2-addition of alkynyl-Pd(II) **143** species to the cyclopropenone carbonyl to afford **144**. This is followed by β-carbon elimination and proto-demetallation to release the product. Although the methodology was only demonstrated on cycopropenone **141**, a good range of terminal alkynes could be employed.

Scheme 34. Cyclopropanols as homoenolate equivalents.



Scheme 35. Pd-catalyzed alkynylation of cyclopropenones.

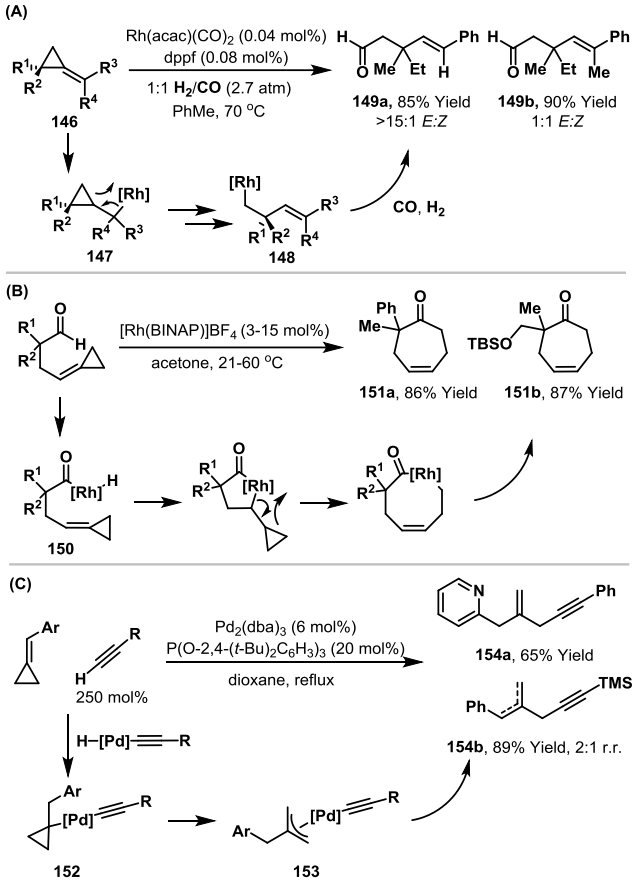


3.2 Cyclopropane-based processes

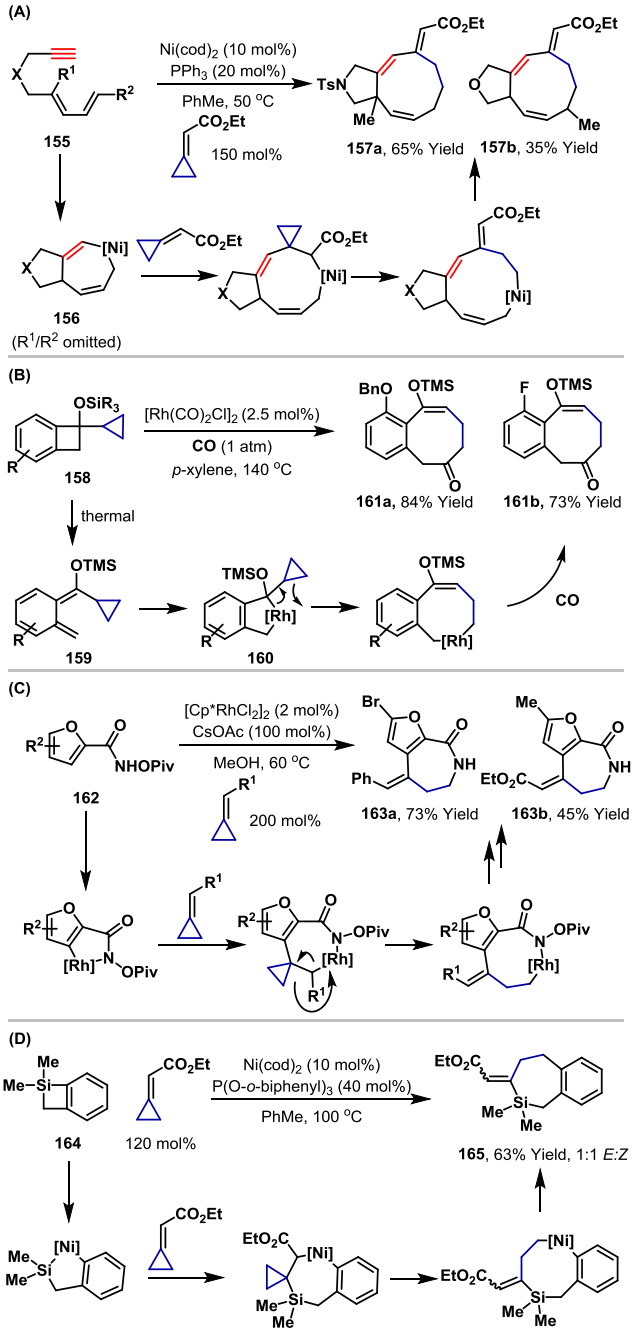
Alkylidenecyclopropanes are also a common substrate class for β-carbon elimination processes, providing complementarity to the C-

C activation methodologies discussed in Section 2.2.[21-23] A range of recent reports have exploited hydrometallation of the alkene unit to set-up the β-carbon elimination step. Marek and Simaan demonstrated hydroformylative conversion of alkylidenecyclopropanes **146** to γ,δ-unsaturated aldehydes (e.g. **149a/b**), bearing β-quaternary stereocenters (Scheme 36A).[152] An example using an enantiopure substrate provided the product with high levels of enantiospecificity. The proposed mechanism invokes initial hydrometallation 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 developed an elegant approach to seven membered rings based on intramolecular Rh-catalyzed hydroacylation of alkylidenecyclopropanes (Scheme 36B).[153] Here, C-H oxidative addition generates **150**, with subsequent hydrometallation, β-carbon elimination and C-C reductive elimination providing cycloheptenone products (e.g. **151a/b**) bearing quaternary stereocenters. Bi-directional 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 hydrometallation step for processes in Schemes 36A and 36B is such that the metal ends up distal to the cyclopropane. Processes involving hydrometallation in the opposite direction have also been developed. Mascareñas, López and co-workers 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).[154] Here, hydrometallation 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 from this provides the products.

Scheme 36. β-Carbon elimination of cyclopropyl moieties triggered by hydrometallation.

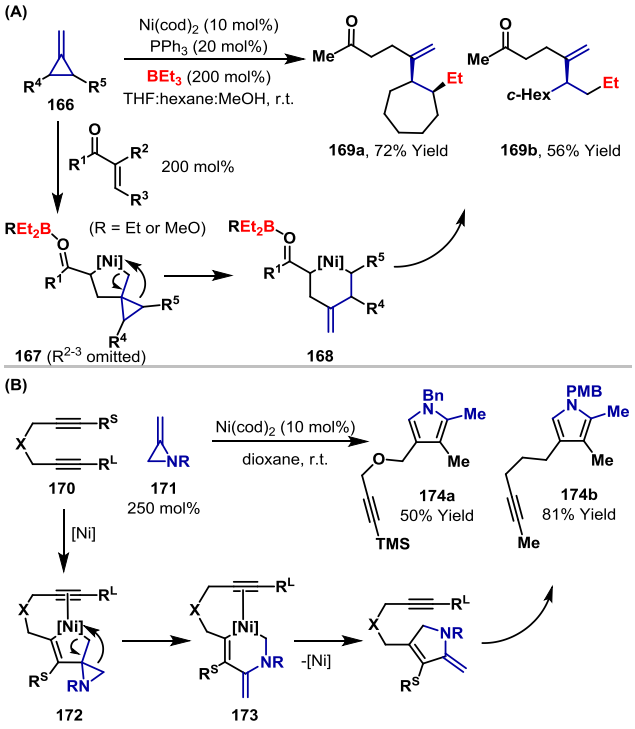


Scheme 37. β-Carbon elimination of cyclopropyl moieties triggered by carbometallation and related processes.



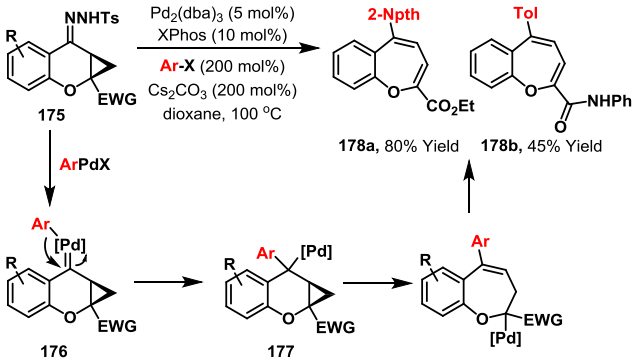
Carbometallation can also be used to set-up the β-carbon eliminations step. This, in principle, allows reactions to be designed around any catalytically generated organometallic species that can undergo alkene migratory insertion. For example, Saito and co-workers outlined an impressive approach to nine membered carbocycles, involving Ni-catalyzed union of yne-dienes and polarized alkylidenecyclopropanes (Scheme 37A).[155] The reaction likely commences with oxidative cyclization of yne-dienes **155** to provide nickelacycles **156**. 1,2-Carbometallation 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 generated embedded alkylidenecyclopropanes **159** by thermal ring opening of benzocyclobutenes **158** (Scheme 37B).[156] 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 8-membered rings (e.g. **161a/b**). C-H activation processes have also been used as starting points. Cui and co-workers demonstrated conversion of furan systems **162** and alkylidenecyclopropanes to seven membered furano-lactams (e.g. **163a/b**), via initial cyclometallation using a Rh(III) catalyst (Scheme 37C);[157] 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 and co-workers showed that a sequence of C-Si oxidative addition and silylmetallation could be used to convert benzosilacyclobutenes **164** and polarized alkylidenecyclopropanes to benzofused silacycles (e.g. **165**) (Scheme 37D).[158]

Scheme 38. β-Carbon elimination of cyclopropyl and aziridinyl moieties triggered by oxidative coupling.



The methodologies in Scheme 37 all involve β-carbon elimination from bicyclic metallacycles en route to bicyclic products. Under Ni-catalyzed conditions, methodologies have been developed which provide access to metalla-monocyclic β-carbon elimination precursors. Using 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 and co-workers (Scheme 38A).[159] 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 $BREt_2$ 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, who developed a pyrrole synthesis by combining methylene aziridines **171** with diynes **170** (Scheme 38B).[161] 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.

Scheme 39. β-Carbon elimination triggered by Pd-catalyzed carbene migratory insertion.



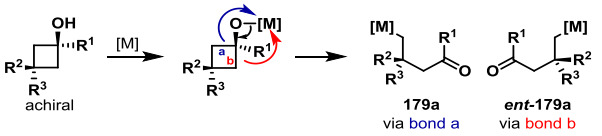
C-C bond forming carbene rearrangements have also been used as the basis for β-carbon elimination methodologies (Scheme 39). Zhou and co-workers showed that tosyl hydrazones **175**, containing a neighboring cyclopropane, are converted to benzoxepines (e.g. **178a/b**) upon exposure to Pd(0)-catalysts and aryl (pseudo)halides.[162] 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 suffers β-carbon elimination and β-hydride elimination to release the product.

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 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.

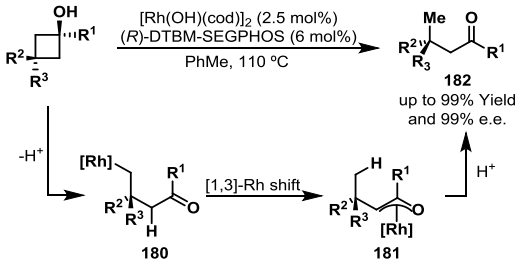
Scheme 40. C-C cleavage via metal-catalyzed β-carbon elimination of cyclobutanols.



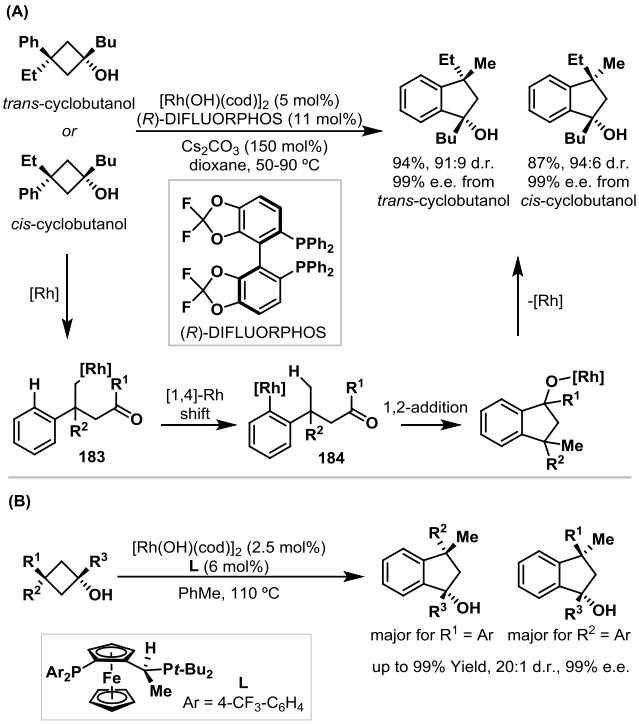
Perhaps the simplest manifestation of the activation mode outlined in Scheme 40 is in processes where the alkyl-metal intermediate undergoes proto-demetallation. In 2010, Cramer and Seiser reported asymmetric reactions of this type, wherein a Rh(I)-catalyst modified with DTBM-SEGPHOS delivered target ketones **182** in high yield and enantioselectivity (Scheme 41).[166] 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 labelling studies revealed that proto-demetallation 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.

The process in Scheme 41 is predated by reports in 2009 from the Cramer and Murakami laboratories which outlined 1,4-Rh-shifts from intermediates **183**.[167,168] This provided the basis for an enantioselective entry to indanols (Scheme 42A/B). Both groups reported that the process is diastereospecific; thus the relative configuration of the product can be changed by switching from the *cis*-cyclobutanol to the *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 in 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.

Scheme 41. Enantioselective synthesis of quaternary stereocenters by β-carbon elimination from cyclobutanols.

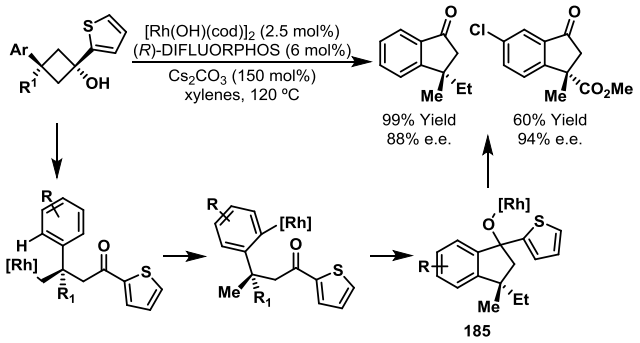


Scheme 42. Enantioselective synthesis of indanols as reported by (A) Murakami and co-workers and (B) Cramer and co-workers.



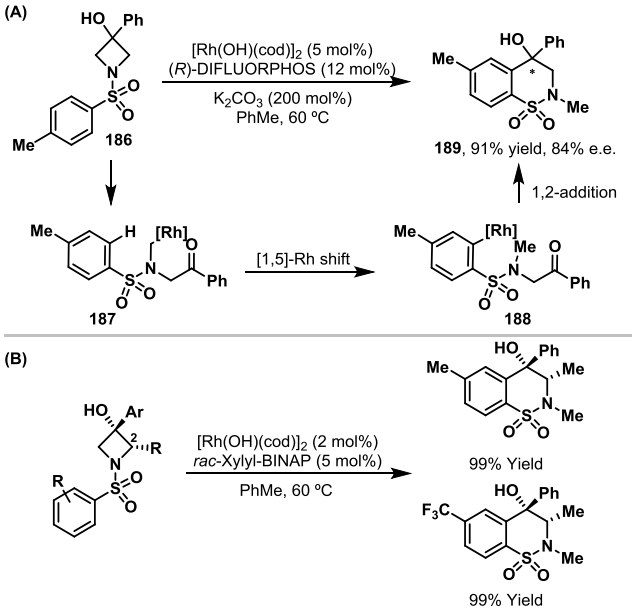
By replacing the R^3 group with an aryl moiety, Cramer and co-workers expanded the scope of the process to the enantioselective synthesis of indanones (Scheme 43).[169] In these cases, a second β-carbon elimination at the stage of **185** releases the product and an aryl-Rh(I) species; presumably, it is this that undergoes proto-demetallation 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 using a distinct C-C activation methodology reported by Murakami and co-workers in 2006.[170]

Scheme 43. Synthesis of indanones as reported by Cramer and co-workers.



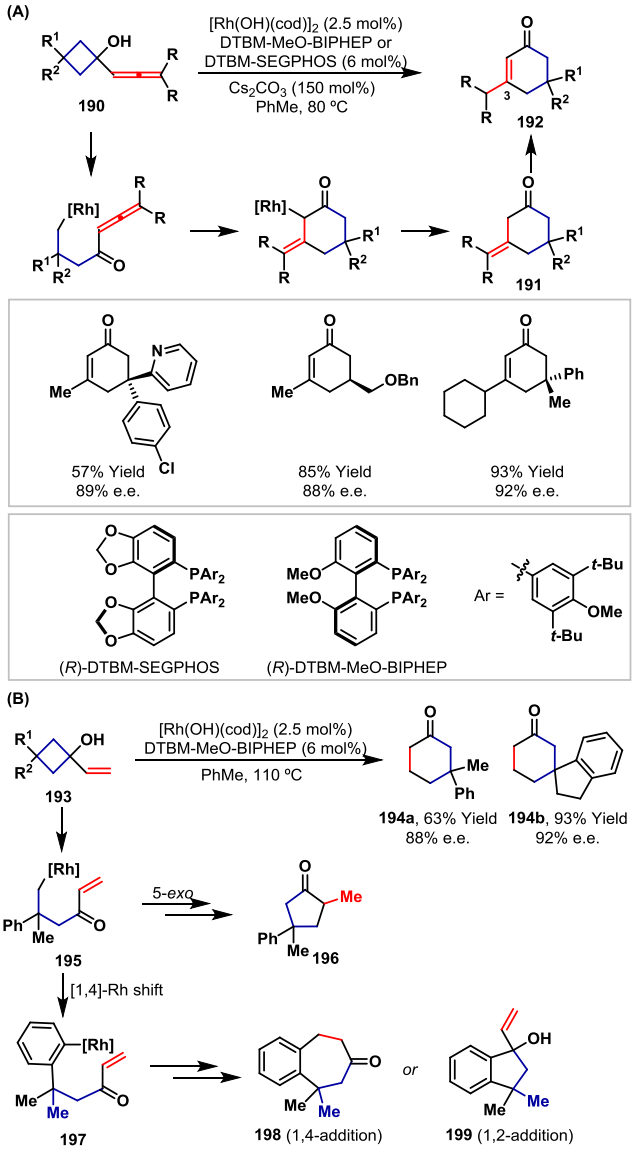
Subsequently, processes involving [1,5]-Rh-shifts after β-carbon elimination (rather than [1,4]-shifts) were developed. Murakami and co-workers showed that rearrangement of azetidin-3-ols (e.g. **186**) led to benzosultams (e.g. **189**) in high yield (Scheme 44A).[171] Here, β-carbon elimination generates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

Scheme 44. Synthesis of benzosultams from azetidinols.



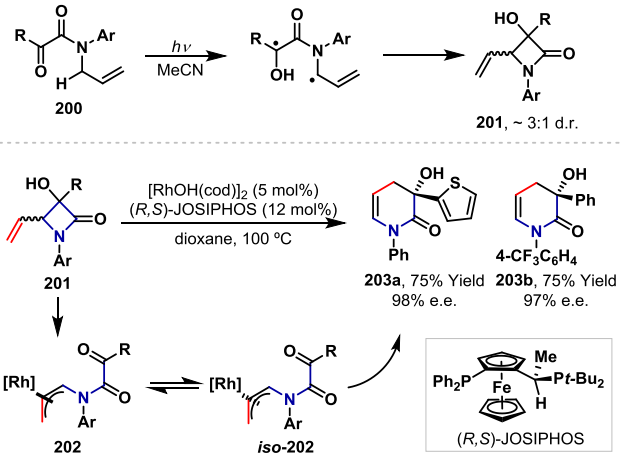
In the methodologies outlined so far, C-C activation is used to generate alkyl- or aryl-Rh(I) intermediates which then form a new C-C bond by 1,2-addition onto a carbonyl group. Cramer and co-workers have shown that the use of allylic *tert*-cyclobutanols enables complementary access to 6-membered rings; here, C-C bond formation occurs via 1,4-addition onto an in situ generated enone (Scheme 45A).[172] In initial studies, it 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 using a variety of chiral ligand systems, with 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 e.g. **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-additions 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.

Scheme 45. Synthesis of cyclohexenones and cyclohexanones from cyclobutanols.



The processes in Scheme 45 employ strained allylic alcohols, but interesting reactivity can also be achieved using homo-allylic 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 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 using (*R*)-JOSIPHOS as ligand. Here, the fluxional nature of allyl-Rh-species **202**/***iso*-202**, which can equilibrate via its 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.

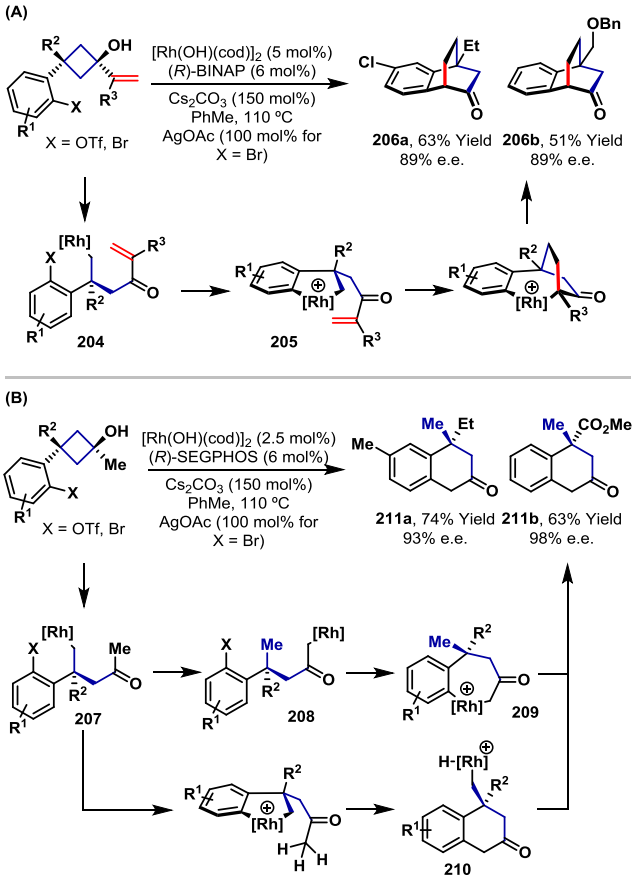
Scheme 46. Piperidinones via sequential light- and Rh-promoted processes.



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, Cramer and co-workers showed that rhodacycles **205** lead to challenging bridged systems (e.g. **206a**/**b**) via carbometallation of the in situ generated enone and subsequent C-C reductive elimination (Scheme 47A).[175] The reaction conditions were optimized both for high enantioselectivity and to suppress an enone aryl-metallation pathway, which is also accessible from **204**. For non-allylic *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 proto-demetallation to release the product

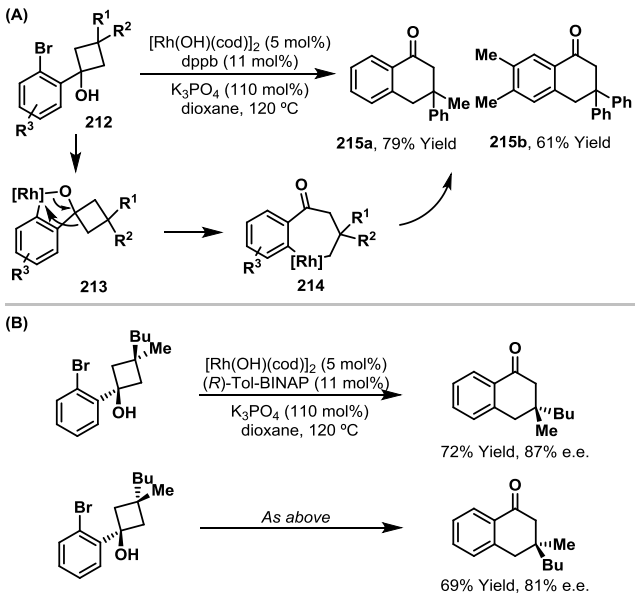
(e.g. **211a/b**). Alternatively, **207** may undergo a [1,5]-Rh shift to generate primary alkyl-Rh intermediates **208**. These can then undergo C-X oxidative addition (to **209**) prior to C-C reductive elimination. Cramer and co-workers outlined the scope of this process and demonstrated high enantioselectivities using (*R*)-SEGPHOS as ligand. The reaction is limited to α-methyl cyclobutanols because of limitations associated with the σ-bond metathesis step.

Scheme 47. (A) Synthesis of bridged ring systems and (B) synthesis of β-tetralones from cyclobutanols.



The studies outlined in Scheme 47 are predated by a report from the Murakami laboratory which demonstrated conceptually distinct C-X activation β-carbon elimination sequences (Scheme 48A).[176] 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 7-ring 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 benzofused piperidin-3-one product. The process is efficient for both electron rich and electron poor arenes and enantioselective variants were demonstrated using (*R*)-Tol-BINAP as ligand (up to 87% e.e.) (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 using the same antipode of the chiral ligand.

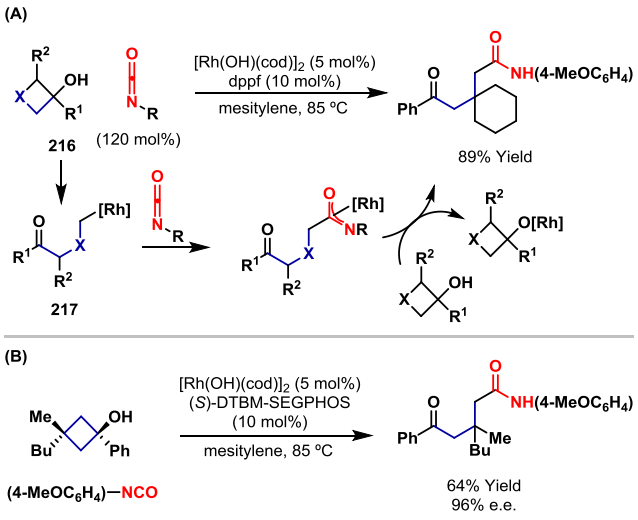
Scheme 48. α-Tetralones by a C-Br/β-carbon elimination sequence.



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 have shown that alkyl-Rh intermediates **217** can be trapped by isocyanates to provide

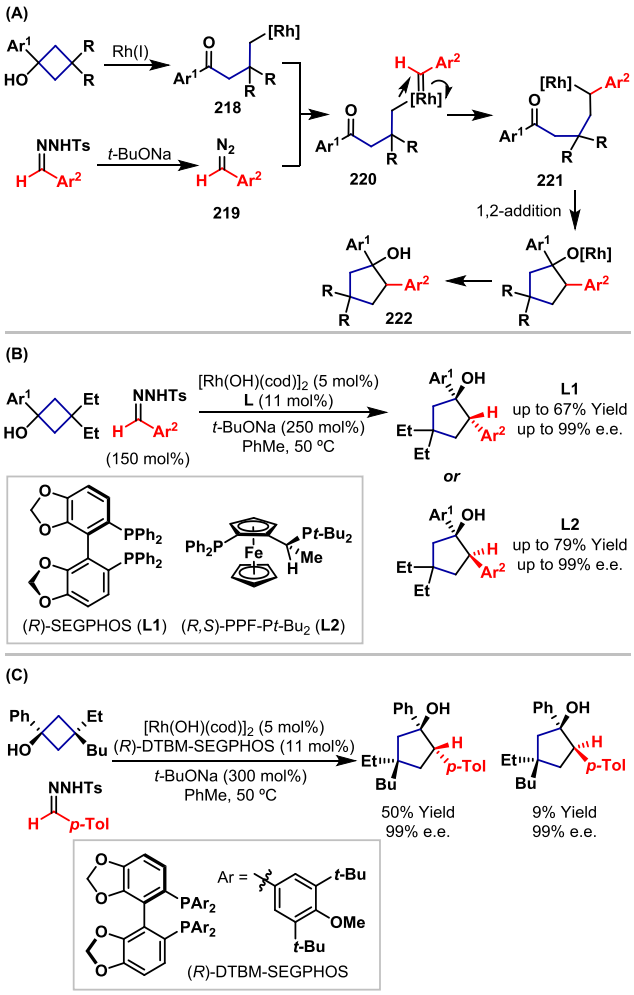
C-carbamoylation products (Scheme 49A).[177] The reaction is notable because competing O-carbamoylation of **216** is avoided. An enantioselective variant was also demonstrated (Scheme 49B).

Scheme 49. β-Carbon elimination triggered C-carbamoylation.



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 in situ generated diazo species **219** 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 in situ generated ketone and subsequent alkoxy exchange with further cyclobutanol releases the product (**222**). By using 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.

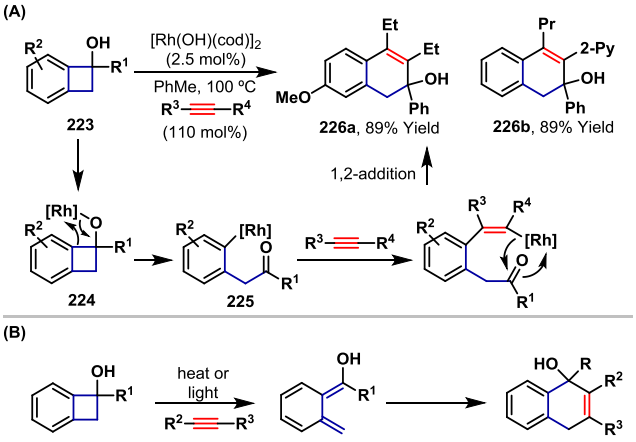
Scheme 50. β-Carbon elimination-carbene insertion cycloadditions.



Murakami and co-workers 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** (Scheme 51A).[179] 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 the method offers complementary regioselectivity to thermally[181] or photochemically[182] driven retrocycloaddition-cycloaddition processes (Scheme 51B). Recently, He and co-

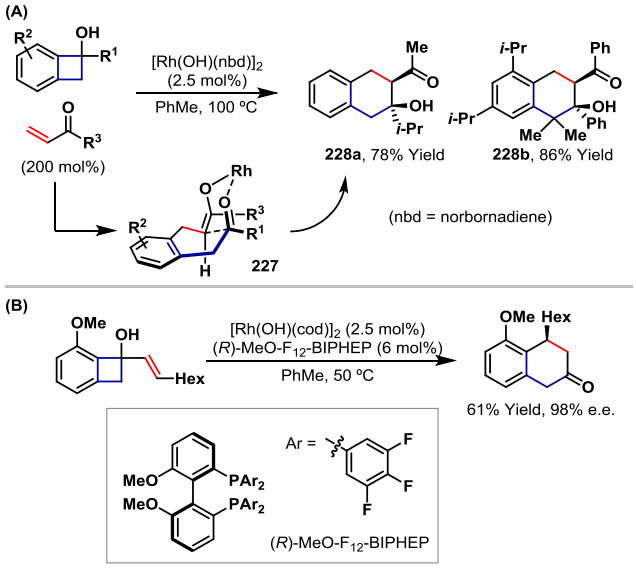
workers reported similar processes using allenes in place of alkynes, which, in turn, leads to products with exocyclic alkenes.[183] In related work, Matsuda and Miura demonstrated formal cycloadditions between cyclobutenols and alkynes.[184]

Scheme 51. β-Carbon elimination triggered (4+2) cycloadditions.



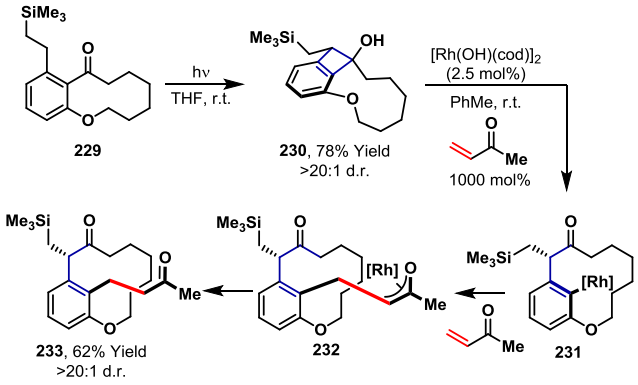
Other classes of intermolecular reaction have been developed. For example, Murakami and co-workers have shown that trapping of β-carbon elimination derived aryl-Rh intermediates **225** with enones provides Rh-enolates **227** (Scheme 52A).[185] These engage the ketone generated during the β-carbon elimination step in an aldol reaction, which proceeds via the indicated chair-like transition state to afford the products (e.g. **228a/b**) in high diastereoselectivity. Enantioselective examples were also disclosed (Scheme 52B).

Scheme 52. β-Carbon elimination triggered conjugate addition-aldol reactions.



An interesting extension of this chemistry involves its application to the diastereocontrolled synthesis of metacyclophanes possessing planar chirality (Scheme 53).[186] Substrates **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 protodemetallation of **232**, product **233**.

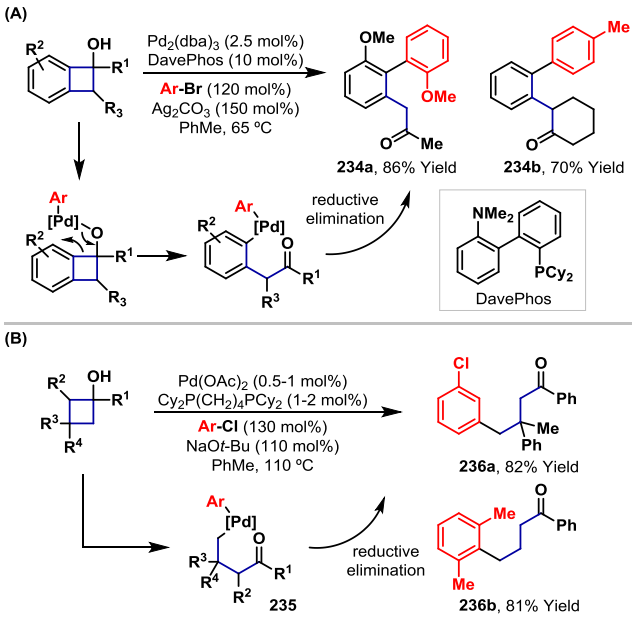
Scheme 53. Photocycloaddition-β-carbon elimination sequence to diastereomerically pure metacyclophanes.



The examples given so far in this section involve Rh-based catalysts, however, there have also been significant developments using Pd-systems. Orellana and co-workers have shown that exposure of

benzocyclobutenols to in situ generated aryl-Pd(II) intermediates leads to a sequence of β-carbon elimination, and C-C reductive elimination to provide *ortho*-arylated products (e.g. **234a/b**) (Scheme 54A).[187] The methodology was applied to the synthesis of phenanthrenes and cyclic imines by designing in situ condensations of the products. Martin and Ziadi 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**).[188] 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.

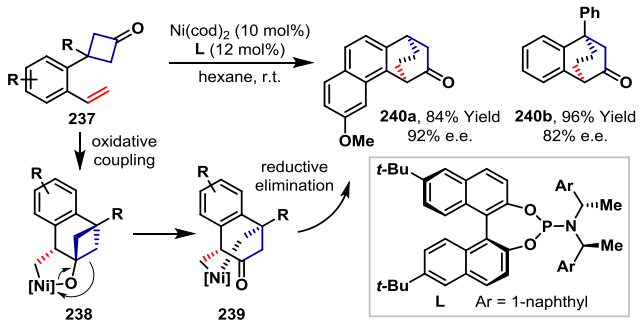


3.4 Cyclobutanone and benzocyclobutenone-based processes

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 complimentary 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 reported enantioselective intramolecular Ni-catalyzed (4+2) cycloadditions of cyclobutanones **237** bearing pendant styrenes (Scheme 55).[191] Oxidative coupling of the ketone and alkene generates oxa-nickelacyclopentanes **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.

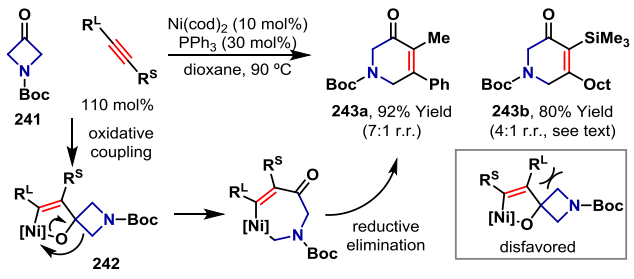
Scheme 55. Oxidative coupling-β-carbon elimination sequence to benzobicyclo[2.2.2]octenones.



Intermolecular processes have been developed using alkynes as a coupling partner. Aïssa and Ho 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

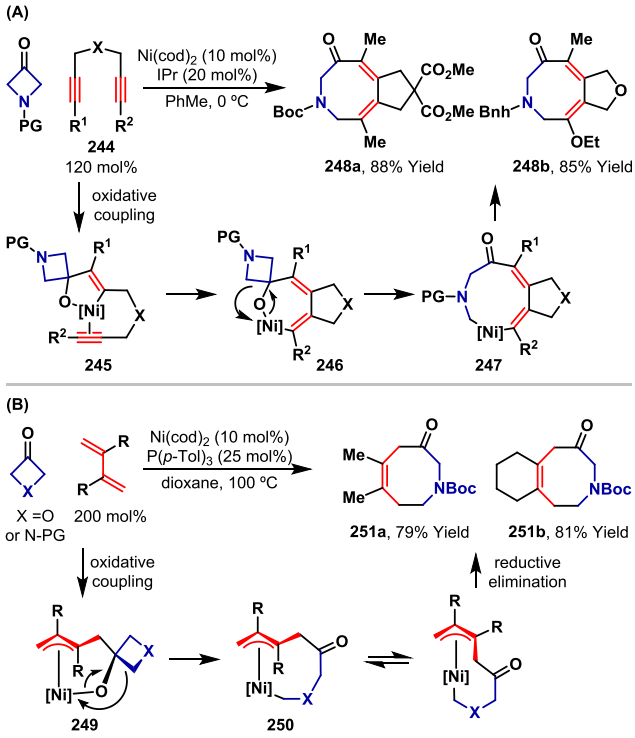
56).[192] At the stage of nickelacycles **242**, steric effects favor an arrangement wherein the larger substituent of the alkyne is placed closer to the Ni-center. For systems where R^1 or R^2 = silyl, electronic effects overturn this selectivity. Related 3-oxetanone based processes were also disclosed. This report was followed quickly by similar studies from the Louie and Murakami groups, with the latter focusing on 2-substituted 3-azetidinones.[193,194] 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 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).[197] Recently, Harrity and co-workers 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.[198]

Scheme 56. Oxidative coupling-β-carbon elimination sequence to piperidine rings by Aïssa and Ho.



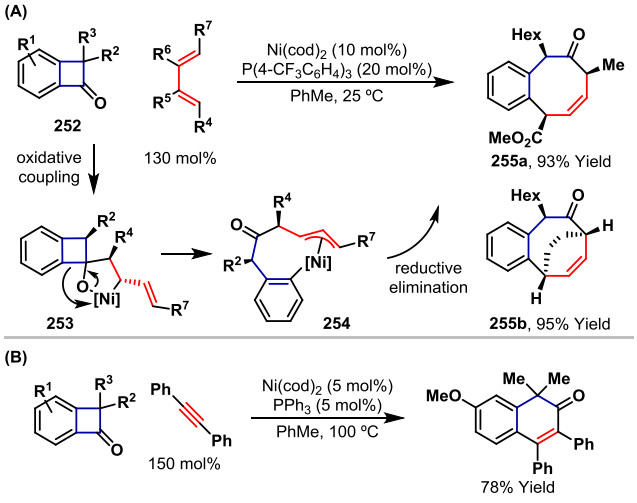
Louie and co-workers have reported (4+2+2) cycloadditions between 3-azetidinones and diynes **244** to generate fused azocane ring systems (e.g. **248a/b**) (Scheme 57A).[199] At the stage of initially generated oxa-nickelacyclopentenes **245** insertion of the tethered alkyne occurs to provide intermediates **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 8-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 accesses using 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 have exploited Ni-catalyzed cycloadditions of benzocyclobutenones to gain access to benzofused 8-membered rings (Scheme 58A).[201] 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.

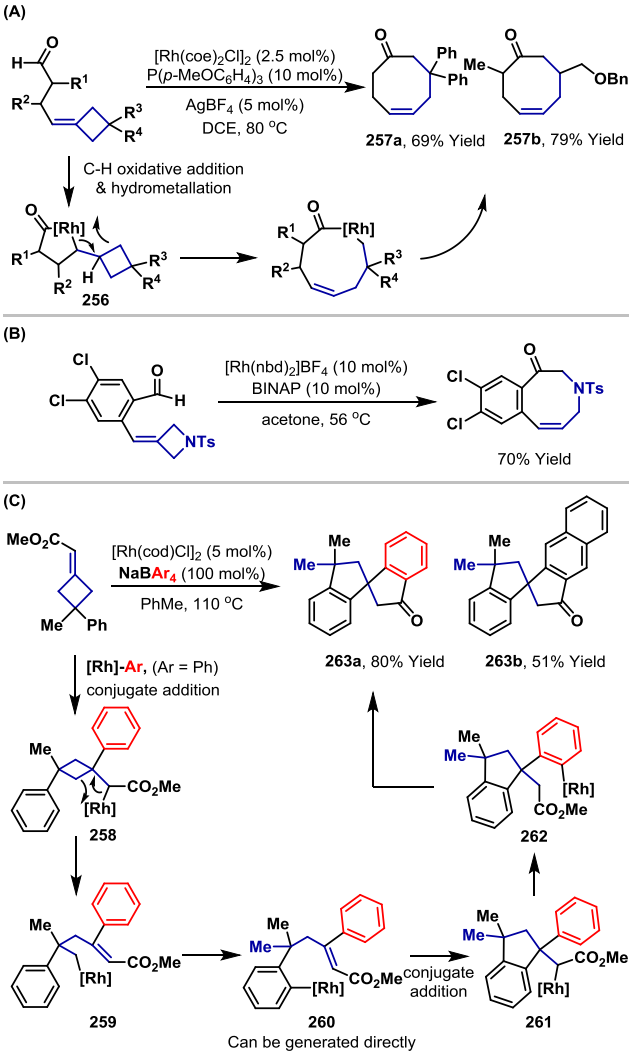
Scheme 58. Oxidative coupling-β-carbon eliminations involving benzocyclobutenones.



3.5 Cyclobutane-based processes

Hydro- and carbometallation 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.

Scheme 59. β-Carbon eliminations triggered by hydro- and carbometallation of alkylidenecyclobutanes.



Aïssa and co-workers have demonstrated intramolecular hydroacylations that generate 8-membered carbocycles (e.g. **257a**/**b**) via collapse of rhodacyclopentanones **256** (Scheme 59A).[202] 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 and co-workers 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).[204] 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 transmetallation from aryl-boronic esters, which resulted in the same 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 the 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 non-activated 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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BIOGRAPHIES

Gabriele Fumagalli was born in Lecco, Italy, in 1987. He completed his MSc in Organic Chemistry in 2011 at the Università Statale of Milan working in the laboratories of Dr Roberto Pagliarin on the synthesis of medicinally relevant molecules. He then moved to Manchester to carry out doctoral studies under the supervision of Prof Michael Greaney, working in the field of photoredox catalysis. After receiving his PhD in 2015 he moved to Bristol to work on C-C activation methodologies and aza-Heck cyclizations in the group of John F. Bower. He is now a postdoctoral associate at the iMed Oncology department of AstraZeneca in Cambridge, UK.

Steven Stanton graduated from the University of St Andrews in 2015 with a MChem degree in Chemistry with Medicinal Chemistry, completing his final year project in the lab of Prof 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 PhD 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 his MSci degree in 2003 from the University of Bristol, where he remained to study for his PhD degree (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. Bower's 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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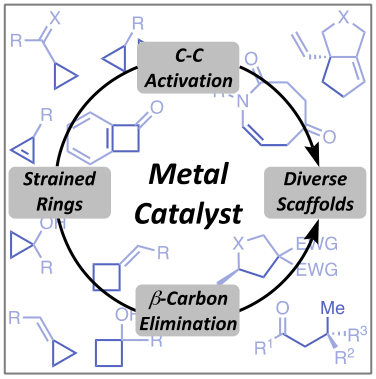
C-C
Activation
Strained
Rings
Metal
Catalyst
Diverse
Scaffolds
β-Carbon
Elimination