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# "Cut and Sew" Transformations via Transition-Metal-Catalyzed Carbon–Carbon Bond Activation

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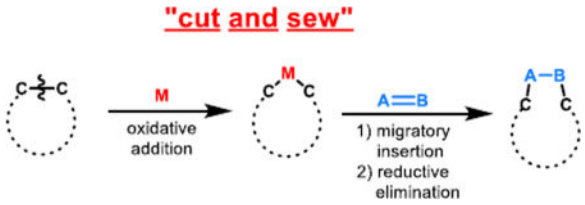
## Abstract

The transition metal-catalyzed "cut and sew" transformation has recently emerged as a useful strategy for preparing complex molecular structures. After oxidative addition of a transition metal into a carbon–carbon bond, the resulting two carbon termini can be both functionalized in one step via the following migratory insertion and reductive elimination with unsaturated units, such as alkenes, alkynes, allenes, CO and polar multiple bonds. Three- or four-membered rings are often employed as reaction partners due to their high ring strains. The participation of non-strained structures generally relies on cleavage of a polar carbon–CN bond or assistance of a directing group.

## Abstract




### Keywords

cut and sew; transition-metal catalysis; carbon–carbon activation; oxidative addition; reductive elimination

## Introduction

The prosperous development of transition-metal (TM) catalysis has dramatically expanded chemists' toolbox, enabling functionalization of many previously considered "inert" chemical bonds.[1] The activation of carbon–carbon single bonds has recently drawn particular attentions,[2] as one less reactive carbon–carbon bond can be converted into two

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more-reactive carbon–metal bonds leading to derivatization of each carbon terminus. Among various C–C activation-based transformations, the insertion of unsaturated moieties into a C–C single bond is of significant interest, because molecular complexity can be quickly built through uniting two fragments and reorganizing bond connections. This process typically involves TM insertion into a C–C bond via oxidative addition, a "cut" process, followed by migratory insertion into a π-unsaturated unit and reductive elimination, a "sew" process (Scheme 1). While there are a number of excellent review articles on C–C activation or cleavage,[2] the main focus of this review is by no means to be comprehensive, but rather to provide a general overview of the development of such "cut and sew" transformations involving TM-catalyzed C–C activation. Formal "cut and sew" reactions, involving a β-carbon elimination process[3] triggered by cyclometalation or nucleophilic addition or intramolecular migration, are also important developments in C–C activation, but not covered here due to space constraint.

As an overview, most "cut and sew" transformations via C–C activation utilize strained three/four-membered ring compounds as substrates, which is largely driven by strain relief when more stable four-/five-membered metallacycles are formed.[4] For example, cyclopropane and cyclobutane[5] derivatives have been frequently employed in a number of cycloadditions serving as C-3 and C-4 components, respectively. Substrates with less or no strain usually incorporate a directing group (DG) or take advantage of a more polar carbon–cyano (CN) bond. Regarding the unsaturate unit that can be "sewed" into a C–C bond, a large emphasis has been given to less polar alkene, alkyne and allene moieties. However, insertion of more polar π bonds, such as aldehydes and imines, has also been demonstrated recently. Apart from regular "cut and sew" processes, carbonylative and decarbonylative transformations that involve gain or loss of CO have also been developed and will be discussed in this article.

## 1. Three-membered rings

Cyclopropanes and their derivatives have been thoroughly explored as synthetically valuable building blocks.[6] Driven by stain relief, these compounds generally undergo smooth ring opening with TMs. While direct "cut and sew" reactions with simple unactivated cyclopropanes remain challenging, vast success has been achieved with more reactive alkylidenecyclopropanes (ACPs), vinylcyclopropanes (VCP) or cyclopropanes with adjacent directing moieties.

### 1.1 ACP (alkylidenecyclopropane)

Cyclopropanes with exocyclic olefins, namely alkylidenecyclopropanes (ACPs), have been widely used in organic synthesis as C-3 building blocks.[7] Early work of TM-catalyzed C–C activation of ACPs was reported by Noyori, Schuchardt, Trost and Tsuji.[8] Based on different metal catalysts applied, two modes of activation with ACPs are possible: palladium and rhodium prefer to insert into the distal $C_3$–$C_4$ bond via oxidative addition, whereas ruthenium and nickel tend to cleave the proximal $C_2$–$C_3$ bond through two plausible intermediates **1** and **2** (Scheme 2). Intermediate **1** involves direct oxidative addition of a TM into the $C_2$–$C_3$ bond; in contrast, intermediate **2** involves cyclometalation between exocyclic

methylene of ACPs, an unsaturated coupling partner, and a TM, followed by a β-carbon elimination process. On the other hand, when the distal $C_3$–$C_4$ is cleaved, the resulting intermediate can be considered as a metal–TMM (trimethylenemethane) species, rendering ACPs as a C–3 component in cycloaddition not only from $C_3$–$C_4$ but also from $C_1$–$C_3$ or $C_1$–$C_4$ positions. In this case, the mechanism may vary based on different substituents. For example, in 2001, Yamamoto reported a Pd-catalyzed heterocycle formation using ACPs and imines as coupling partners (Scheme 3a).[9] In their proposed mechanism, palladium species cleaved the distal $C_3$–$C_4$ bond and led to the palladacyclobutane intermediate **3**, where migratory insertion with the imines occurred at the $C_1$ position to form the π-allyl species. After reductive elimination, pyrrolidine derivative **4** was afforded, with $C_1$ and $C_3$ incorporated in the five-membered ring (Scheme 3b). However, in one of their examples, a regioisomer from cycloaddition at $C_3$ and $C_4$ positions was observed. It was reasoned that due to the bulky *t*Bu substituent in the imine substrate, the migratory insertion occurred at the less sterically hindered $C_3$ position instead (Scheme 3c). While there are numerous transformations with ACPs, in this section only the reactions that clearly fall into the "cut and sew" portfolio are discussed.

**a. Distal C–C Bond Cleavage—**In 1988, Motherwell and coworkers studied intramolecular [3+2] cycloaddition of diphenylmethylenecyclopropanes with alkenes and alkynes (**5** and **6**, Scheme 4).[10] With a palladium catalyst, the ACP moiety underwent a "cut and sew" transformation through cleavage of the distal C–C bond. The fused 5,5- and 5,6-bicycles were obtained in moderate yields. Shortly after, the same group expanded this method to methylenecyclopropanes (MCPs, **7**).[10b] Additional phosphite ligand was employed to facilitate reductive elimination.

In 1991, when the Motherwell group explored the aforementioned "cut and sew" reaction in the absence of Thorpe–Ingold effect, heteroatom was found to assist the transformation by chelating to the metal catalyst (**8** and **8'**, Scheme 5).[11] In sharp contrast to substrate **9** (R = H) that failed to provide any bicyclic products, substrate **10** (R = OBn) having a chelating oxygen atom afforded the desired adduct in a moderate yield.

The Lautens group later studied the stereochemistry of this reaction.[12] When ACPs **11** containing $C_3$ stereocenters were employed, retention of the stereo-information was obtained (Scheme 6). The acetylenic substituent has a marginal effect on the stereoselectivity.[13] The reaction mechanism was proposed to initiate from the coordination of the alkyne to Pd(0), which is followed by distal C–C activation and alkyne migratory insertion (Scheme 7). A σ-π-allyl interconversion then occurs in intermediate **12** and leads to exchange of the two carbons supported by deuterium-labeling experiments. In 1996, the Lautens group further demonstrated that the intramolecular [3+2] cycloadditions with tethered alkenes were also stereospecific.[14]

**b. Proximal C–C Bond Cleavage—**In 2004, the Saito group reported that cyclopropylideneacetates **13** can couple with two equivalents of alkynes to provide cycloheptadienes using $Ni(COD)_2/PPh_3$ as a catalyst (Scheme 8a).[15] In their following reports, a variety of internal and terminal alkynes bearing different electron properties were successfully coupled under similar reaction conditions.[16] The replacement of alkyne

moieties with tethered diynes[17] or dienes[18] were later realized, affording moderate to good yields and high regioselectivity (Scheme 8b).

An interesting variation was reported when the [3+2+2] cycloaddition was investigated between **13** and two different alkynes (Scheme 9).[19] Surprisingly, the cycloaddition proceeded in a high regioselective manner. In addition, the [3+2+2] cycloaddition also occurred smoothly with conjugated diynes[20] or enynes[21].

In 2010, López and Mascareńas extended the [3+2+2] cycloaddition reaction with tethered substrates (Scheme 10).[22] The ACP-alkyne-tethered substrates **14** underwent [3+2+2] cyclization with electron deficient alkenes, while the use of unactivated alkenes resulted in recovery of the starting material. Deuterium-labeling experiments and DFT calculation studies both supported a pathway involving oxidative addition of Ni(0) into the proximal C–C bond (*vide supra*, intermediate **1**, Scheme 2). In addition, substrates tethered with all the three components, ACP-alkyne-alkene (or another alkyne), can be employed, leading to efficient construction of 6,7,5- fused tricycles.[23]

Similarly, an intramolecular cycloaddition between ACPs and alkynes was reported by the Zhang group in 2011, in which the proximal C–C bond was cleaved (Scheme 11).[24] This transformation provides a unique approach to prepare cyclopenta[a]indene derivatives.

A Ni-catalyzed [3+2] cycloaddition between ACPs **16** and external olefins was reported by the Bhargava group in 2015.[25] When bis(alkylidenecyclopropanes) were employed as substrates, a variety of electron-deficient olefins were coupled, providing the mono adduct in moderate to excellent yields (Scheme 12a). The afforded 2,3-disubstituted alkylidenecyclopentane **17** clearly indicated the proximal C–C bond cleavage rather than distal cleavage. The coordination with the alkenyl bond from the neighboring ACP moiety as shown in intermediate **18** was proposed to account for the reactivity. This hypothesis was supported by control experiments where substrates lacking the second tethered ACP resulted in no reaction (Scheme 12b).

### 1.2 Simple cyclopropane

The first TM insertion into cyclopropane was reported by Tipper in 1955.[26] Although different TMs have been extensively studied towards the activation of cyclopropane derivatives, their utilization in a “cut and sew” transformation was less-commonly seen in literature, majorly due to the facile β-hydrogen elimination side reaction from the metallacyclobutane complex.[27] Narasaka and coworkers in 1999 reported the first rhodium-catalyzed carbonylative addition with a tethered cyclopropane and alkyne (Scheme 13).[28] Though the presence of CO suppressed side-reactions, the reactions proceeded more slowly under increased CO pressure. The stereochemistry information in the starting material was delivered to the product and the cyclopropane cleavage occurred preferentially at the less hindered C–C bond. The proposed mechanism involved oxidative addition of Rh(I) into the cyclopropane C–C bond directed by the alkyne moiety (cf intermediate **19)**.

In 2006, the Montgomery group discovered a Ni-catalyzed dimerization of cyclopropyl ketones (**20**, Scheme 14).[29] Using $Ni(COD)_2$ as a precatalyst and a *N*-heterocyclic carbene

(NHC) ligand **21**, trisubstituted cyclopentane derivatives with two carbonyls in *trans*-configuration were obtained in good yields and excellent diastereoselectivity. Regarding the reaction pathway, one cyclopropyl ketone was proposed to first undergo a Ni-catalyzed isomerization to conjugate enones, which then underwent a [3+2] cycloaddition with another equivalent of cyclopropyl ketone to afford the product. Based on this mechanistic hypothesis, external enones **22** were found to directly couple with cyclopropyl ketones. Good yields and excellent regioselectivity were obtained when the concentration of the enone were kept low via slow addition; titanium salts were added to accelerate the transformation. While cyclopropyl aldehydes failed to react, aldimines **23** were found to afford the desired [3+2] cycloadducts in good yields.[30] In contrast, the two carbonyl groups in **24** were in *cis*-configuration, which was attributed to the ease of epimerizing the α-position of the aldehyde moiety.

The coupling of cyclopropyl ketones and alkynes was studied by the Ogoshi group in 2011.[31] $Me_2AlCl$ was employed as a Lewis acid cocatalyst in addition to the Ni catalyst (Scheme 15). The mechanism was proposed to initiate from coordination of the alkyne and ketone moieties to Ni. Assisted by $Me_2AlCl$, oxidative addition occurs to cleave the proximal C–C bond of the cyclopropyl group to form intermediate **25** where migratory insertion into alkynes leads to intermediate **26**. Due to that 1,2-*trans*-disubstituted cyclopropanes afforded both 1,4-*trans* and 1,4-*cis*-products, an interconversion between intermediates **26** and **27** was proposed to occur prior to direct reductive elimination.

In 2013, the Bower group developed an intramolecular carbonylative “cut and sew” transformation of aminocyclopropanes with alkynes (**28**, Scheme 16).[32] The choice of the amine protecting group is crucial as it needs to be able to coordinate with the metal and direct the C–C activation step while labile enough to be substituted by the alkyne for sequential migratory insertion. The urea group ($R = NMe_2$) was found to be optimal to afford high reactivity when the substrate was treated with $[Rh(COD)Cl]_2$ an electron-deficient mono-dentate phosphine ligand under 1 atmosphere of CO. For substituted cyclopropyl substrates, C–C bond cleavage occurred predominately at the less hindered side (e.g. **29** and **30**, Scheme 16).

The Bower group further extended the intramolecular [3+2+1] transformation to the coupling with alkenes (Scheme 17a).[33] The carboxybenzyl (Cbz) group was found to be a more effective DG, and various *trans*-bicycles were provided. Substituted cyclopropanes were investigated where *trans*-1,2-disubstituted and trisubstituted cyclopropyl groups (**31** and **32** respectively) can smoothly deliver the desired products in good yields. Moreover, compared with the previous conditions,[32] the newly developed cationic rhodium condition was later proved to significantly increase the reactivity for the urea-directed intramolecular carbonylative [3+2+1] reactions with alkynes (Scheme 17b).[34]

Recently, the same group successfully expanded the transformation to the use of aminomethylcyclopropanes **33** as substrates for construction of perhydroisoindoles **34** (Scheme 18).[35] Similarly, the carbonyl unit in the nitrogen protecting group directed C–C activation to provide the six-membered ring intermediate **35**, whereas due to the added methylene unit, the β-hydrogen elimination became the major side reaction. Compared with

the cationic rhodium system, a neutral rhodium precursor efficiently suppressed the β-hydride elimination, presumably due to the lack of a vacant coordination site.

### 1.3 Vinylcyclopropane (VCP)

Vinylcyclopropane is among the most extensively explored three-membered ring system.[36] Typically, VCPs are classified based on their substitution positions. Terms such as 1-ene-/2-yne/β-yne-VCPs are often seen from literatures (Scheme 19). VCP has been frequently employed as a five-carbon component in cycloadditions, which involve cyclometalation then β-carbon elimination or oxidative addition then ring expansion (Scheme 20).[37] On the other hand, VCPs that contain strong electron-withdrawing groups can be ionized by TMs (e.g. palladium) to generate a zwitterionic π-allyl intermediate, which can then couple with Michael acceptors (Scheme 21).[38,39] Given that these transformations have been nicely reviewed previously and their mechanisms do not cleanly fall into the “cut and sew” scope, detailed discussions of these reactions will not be provided here. Some typical examples with VCPs as a three-carbon component are summarized.

In 2008, Yu and co-workers reported the first Rh-catalyzed intramolecular cycloaddition of 2-ene-VCPs **36** with a tethered alkene moiety (Scheme 22).[40] With a rhodium catalyst, a myriad of *trans*-1,2-disubstituted VCPs reacted to provide 5,5-bicycles in good yields. The use of a cationic rhodium catalyst, *in situ* generated from $[Rh(CO)_2Cl]_2$ and AgOTf, proved to give increased reactivity. The chirality information from the starting material can also be delivered to the bicyclic products (such as **37** and **38**, Scheme 22). However, *cis*-1,2-disubstituted VCP **39** afforded [5+2] cycloadducts exclusively. The difference in reactivity between the *trans*- and *cis*-substrates was rationalized based on the distance of the two carbons that can undergo reductive elimination in these reactions.

Two years later, the same group achieved the first intramolecular [3+2] cycloaddition of 1-yne/ene -VCPs (Scheme 23).[41] The desired bicyclic products were provided upon employment of a cationic rhodium/phosphine complex. Functional groups, such as esters and different heteroatom tethers, as well as 1-yne/allene-VCPs were well tolerated. The necessity of the vinyl group in the cyclopropane ring activation was supported by control experiments. The DFT studies suggested that the catalytic cycle starts from complexation of the rhodium catalyst to the vinyl group of the VCP, followed by insertion of Rh(I) into cyclopropane C–C bond to give π-allyl rhodium species **41** (Scheme 24). Subsequent migratory insertion into the tethered alkene/alkyne and reductive elimination provide the [3+2] cycloadduct.[42]

The asymmetric version of the reaction was also realized using *in situ* generated cationic rhodium in combination with chiral (*R*)-$H_8$-BINAP ligand (Scheme 25).[43] Further DFT studies suggested that the enantioselectivity was controlled by the alkyne-insertion step.

A novel [3+2+1] cycloaddition of 1-yne/ene-VCPs was also realized when the reactions were carried under a CO atmosphere (Scheme 26).[44] Cyclohexanone/cyclohexenone products **42** bearing various functional groups were afforded in good yields. The reaction was proposed to follow the similar mechanism as the one described in Scheme 24. It is worthy to note that this [3+2+1] method has been effectively employed in the total synthesis

of (±)-α-agarofuran and formal syntheses of gracilamine, (±)-galanthamine and (±)-lycoramine.[45]

In addition, the Yu group further found that, when the alkyne moiety of the substrate has a bulky substituent, carefully tuning the reaction conditions (e.g. solvent and CO pressure) led to selective formation of a distinct multifunctional angular tricyclic 5/5/6 skeleton (**43–45**, Scheme 27) through insertion of two CO units.[46] This reaction can be considered as a formal [5+1]/[2+2+1] cycloaddition, though control experiments and DFT studies suggest a more complex mechanism involving sequential migratory insertion into alkyne, CO, alkene, and then CO after C–C cleavage. Interesting, when a longer tether was used, only the normal [3+2+1] product, e.g. **46**, was observed.

In 2010, Yu and coworkers reported the first [3+2] cycloaddition with α-ene-VCPs (**47**, Scheme 28).[47] Unlike β-ene-VCPs that tends to give [5+2] cycloaddition,[48] a [3+2] reaction was observed exclusively with the α-ene-VCPs. Using a cationic Rh(I)-phosphine complex as the catalyst, 5,6- and 5,7-bicycles were formed in good yields and excellent diastereoselectivity. Tethered alkynes didn't result in any desired [3+2] cycloaddition due to a rapid intramolecular cyclopropanation (**48**, Scheme 28).

The Matsubara group in 2014 explored a Ni(0)-catalyzed intermolecular [3+2] cycloaddition between VCPs **49** and allenes (Scheme 29).[49] The use of $Ni(COD)_2$ and $PMe_3$ proved to be an optimal combination. Allenes bearing a variety of functional groups were well tolerated. The reaction was proposed to go through oxidative addition of Ni(0) to cleave the cyclopropyl C–C bond, followed by allene migratory insertion and reductive elimination to afford the five-membered carbocycle.

### 1.4 Miscellaneous

In addition to the rich transformations discussed above, "cut and sew" transformations with other three-membered rings are also known. Due to the high ring strain, cyclopropenes and cyclopropenones[50] have also participated in various TM-catalyzed reactions.[51] For example, in 1976 Baba and co-workers reported a cycloaddition of diphenylcyclopropenone **50** and *N*-sulfinylamine **51** with stoichiometric $Ni(CO)_4$ (Scheme 30).[52] The reaction was proposed to proceed through a six-membered metallacycle intermediate **52**, in which an exchange of the S=O unit with CO from $Ni(CO)_4$ occurs to provide the maleimide product.

In 2006, an intramolecular [3+2] cycloaddition between cyclopropenones and alkynes was reported by Wender and coworkers, which offers a new way to prepare cyclopentadienones (Scheme 31). $[RhCl(CO)_2]_2$ was found to be an efficient precatalyst; a wide range of internal alkynes, such as aryl and alkyl-substituted alkynes, enynes, heteroaryl alkynes and benzynes, were well compatible. The cyclopentadienone products were afforded in good yields and excellent regioselectivity.[53]

Recently, the Wang group realized a Rh-catalyzed intramolecular carbonylative cycloaddition between cyclopropenes and tethered alkenes or alkynes (**53** and **54** respectively, Scheme 32).[54] Under 1 atmosphere CO, a myriad of ene/yne-cyclopropene substrates underwent a [3+2+1] cycloaddition and provided the bicyclic scaffolds in good

yields. For tethered alkene derivatives, all the cyclohexenone derivatives were obtained as single diastereomers. The mechanism was proposed to initiate from alkene or alkyne-directed cleavage of the cyclopropene C–C single bond, followed by subsequent carbonylation, migratory insertion and reductive elimination.

## 2. Four-membered rings

Four-membered ring compounds are another important class of substrates that has been profoundly explored for C–C activation. The “cut and sew” transformations with cyclobutanones, cyclobutenones, biphenylenes and their derivatives have been developed, which have led to a diverse range of polycyclic scaffolds.

### 2.1. Cyclobutanone

Early works on TM-catalyzed C–C activation of cyclobutanones were reported by Ito and Murakami where they enabled oxidative addition of rhodium into the C–C bond adjacent to the carbonyl group.[2m,55] Ring-opening or decarbonylation products were obtained. These seminal examples paved the way for the development of “cut and sew” chemistry with cyclobutanones. In 2002 the same group reported a Rh(I)-catalyzed activation of styrene-tethered cyclobutanones to give bicyclo[3.2.1]octanes (Scheme 33).[56] The mechanism was proposed to start with oxidative addition of Rh(I) into the cyclobutanone α-C–C bond followed by alkene migratory insertion and reductive elimination (Scheme 34).

The asymmetric version of this transformation was later revealed by Cramer and coworkers in 2014 through a chiral rhodium-catalyzed enantiotopic C–C cleavage. Two sets of conditions were made available: first they developed a zwitterionic catalytic system and the reaction proceeded at lower reaction temperature with moderate enantioselectivity (Scheme 35a).[57] Shortly after, they discovered that the use of DTBM-SEGPHOS (**56**) as the ligand can induce exceptionally high enantioselectivity (Scheme 35b). [58] Under the latter conditions, mono-, di- and tri-substituted alkenes can be used as the coupling partners.

One challenge to expand the scope of the “cut and sew” coupling between cyclobutanones and olefins is the competing decarbonylation: upon Rh(I) oxidative addition into cyclobutanone C–C bond if the olefin insertion is slow, the decarbonylation would dominate and lead to forming cyclopropane or propene (Scheme 36).[55,56] To address this issue, Ko and Dong devised a strategy that uses 2-amino-3-picoline **57** as a cocatalyst (previously employed by Jun in activation of non-strained ketones)[59] to *in situ* protect the cyclobutanone carbonyl group and simultaneously serve as a DG (Scheme 37a).[60] The use of electron-deficient mono-dentate phosphine ligand $P(3,5\text{-}C_6H_5(CF_3)_2)_3$ was also found critical for the success of the reaction. Under these conditions, a range of 6,6- and 5,6-fused bicyclic structures can be afforded. Mono-, and 1,1- and 1,2-disubstituted alkenes were used as coupling partners. Promising level of enantioselectivity was also achieved using a chiral phosphoramidite ligand (Scheme 37b).

When allenes were used as the coupling partner for a “cut and sew” reaction with cyclobutanones, an unexpected [4+1] cycloaddition was observed by Zhou and Dong.[61] Formally serving as a vinyl carbenoid equivalent, the central carbon of the tethered allene

inserted into the cyclobutanone α-C–C bond providing a [4.2.1]-bicyclic skeleton **59** (Scheme 38). The corresponding [4+2] product was observed as a minor product (Scheme 39). The enantioselective variant was also realized when ligand **60b** was employed. Both 1,3-di- and 1,1,3-tri-substituted allenes were competent for this transformation, while mono-substituted allenes tended to cause dimerization of the substrate. The proposed mechanism initiates from rhodium oxidative addition into the α-C–C bond of cyclobutanone derivatives, followed by allene migratory insertion (Scheme 39). The resulting rhodacycle **61** then undergoes β-hydrogen elimination/reinsertion to generate intermediate **62** or **63**, where the following reductive elimination provides the [4+1] cycloadduct **59**.

More recently, an intramolecular formal [4+2–1] cyclization between cyclobutanones and tethered olefins was realized by Dong and coworkers (Scheme 40).[62] While decarbonylation of cyclobutanones to give cyclopropanes and the regular [4+2] process are highly competitive side reactions (*vide supra*, scheme 36), use of a bulky monodentate XPhos (2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) ligand promoted an unusual [4+2–1] pathway. Control experiments indicated that the reaction is unlikely to go through a cyclopropane-mediated [3+2] pathway (from decarbonylation of the cyclobutanone) or decarbonylation of the [4+2] product; instead, the [4+2–1] reaction was proposed to arise from direct cyclobutanone C–C cleavage, CO extrusion, olefin migratory insertion, and reductive elimination. The synthetic utility of the method was exemplified in the synthesis of antifungal drug tolciclate (Scheme 41).

In addition of using non-polar 2π coupling partners, Cramer and coworkers developed a novel carbonyl insertion variant to obtain bridged bicyclic lactones (**65**) in high enantioselectivity, a reaction analogous to the Tishchenko disproportionation (Scheme 42).[63] The reaction was found to tolerate a number of cyclobutanone-substituted moieties as well as aldehyde and ketone insertion partners. Aldol condensation and cyclopropane formation from decarbonylation of cyclobutanones were observed as common side reactions. The proposed mechanism corresponds to the previous styrene insertion; formation of rhodacycle **66** leads to the subsequent insertion of the pendant carbonyl (Scheme 43).

### 2.2 Cyclobutenone and Cyclobutendione

Early work from the Liebeskind group shows that TMs, such as nickel, iron, rhodium and cobalt, can insert into cyclobutenedione **67** to form a five membered metallacycle **68**, which can then couple with an alkyne to yield substituted quinones (Scheme 44).[64] In attempts to expand this chemistry to cyclobutenones and benzocyclobutenones for syntheses of phenols and naphthols, the use of Rh(I) led to the isolation of a five-membered rhodacycle **69**, which was inert with alkynes (Scheme 45).[65] Later work from the same group found that the use of Co(I) instead was capable to induce subsequent coupling with alkynes.[65b,66] A year later, the catalytic “cut and sew” transformation between cyclobutenones **70** and alkynes was realized with Ni(0), and the regioselectivity of the insertion product **71** can be controlled by using heteroatom-substituted alkynes (such as **72**).[65b,67] More recently, Auvinet and Harrity extended the scope of the nickel-catalyzed alkyne insertion to include alkynyl boronates (Scheme 46).[68] The regioselectivity of the reaction is influenced by the substituents on the

alkynyl boronates: forming regiosomer **73** is favored for alkynyl-bornoates with a $sp^3$ substituent, whereas those with a $sp^2$ substituent prefer to give regiosomer **74**.

In addition to coupling with alkynes, Kondo, Mitsudo and coworkers successfully expanded the substrate scope to electron-deficient olefins, norbornene, and ethylene using rhodium and ruthenium catalysts. First, $Ru_3(CO)_{12}$ was discovered to induce a decarbonylative coupling of cyclobutenediones **75** with norbornene to yield cyclopentenone **76** (Scheme 47, path a).[69] When higher carbon monoxide pressure was applied, direct insertion to give hydroquinone product **77** was observed (Scheme 47, path b). The proposed mechanism is similar to the aforementioned alkyne insertion into cyclobutenones (*vide supra*, Scheme 45).

Later, cyclobutenone activation by $[Rh(CO)_2Cl]_2$ was found to result in either direct norbornene insertion or decarbonylative insertion (Scheme 48, paths a and b respectively); similar to their previous work, the carbon monoxide pressure was the key factor to control the reaction selectivity.[70] A notable side reaction was cyclobutenone dimerization (Scheme 49). The mechanism was proposed to involve Rh(I) insertion into cyclobutenone **78** to give metallacycle **79**. Migratory insertion with the olefin gives fused ring **80**, which can undergo decarbonylation under argon atmosphere followed by reductive elimination to give cyclopentene **81**, or direct reductive elimination under carbon monoxide atmosphere to provide cyclohexenone **82** (Scheme 50). The work was later expanded to insertion of electron-deficient alkenes to yield 2-substituted phenol derivatives (**83**, Scheme 51).[71]

An intramolecular decarbonylative coupling between cyclobutenediones and olefins were reported by Yamamoto and coworkers (Scheme 52).[72] Derived from squaric acid, substrate **84** underwent C–C cleavage between the two carbonyls, followed by decarbonylation and alkene insertion, to afford a range of fused cyclopentenone bicycles **85**, which is catalyzed by Wilkinson's complex or *in situ* generated Wilkinson's complex.

The Dong group has been focusing on developing intramolecular "cut and sew" transformations with benzocyclobutenones. While cleavage of the benzocyclobutenone $C_1$–$C_8$ bond is kinetically favored, the work by Xu and Dong showed that benzocyclobutenone substrate **86** can undergo cleavage of the proximal $C_1$–$C_2$ bond using Rh(I) as the catalyst (Scheme 53).[73] Mono-, di-, and tri-substituted alkenes can be coupled, leading to various benzo-fused tricyclic scaffolds **87** with high functional group tolerance. The use of $ZnCl_2$ as a Lewis acid cocatalyst was found to be critical for more challenging substrates, such as those with aryl olefins and longer tethers (Scheme 54). Control experiments showed that no desired insertion product was obtained in the absence of the rhodium catalyst either in the presence or absence of $ZnCl_2$. A more detailed DFT studies suggest a stepwise $C_1$–$C_2$ activation pathway involving cleavage of the $C_1$–$C_8$ bond followed by a decarbonylative CO migration (Scheme 55).[74]

Stimulated by forming chiral all-carbon quaternary centers, in 2012 the Dong group developed an enantioselective version of the transformation using $[Rh(COD)Cl]_2$ and DTBM-SEGPHOS (**56**) as the metal-ligand combination (Scheme 56).[75] High enantioselectivity was obtained at relatively high reaction temperature. A reductive dearomatization protocol was developed to access saturated fused chiral "half-cage"-like

compounds **88** (Scheme 57). Selective hydrogenation from the convex face afforded saturated fused compounds as single diastereomers.

To enable insertion of sterically hindered alkenes, a more reactive catalyst system was discovered by Xu and Dong using $[Rh(CO)_2Cl]_2$ and $P(C_6F_5)_3$ (Scheme 58a). The increased π-acidity of the metal center enhanced its binding affinity with the alkene moiety. A number of tri-substituted alkene substrates, non-reactive under the previous conditions, were efficiently coupled with benzocyclobutenones (such as **89**). Using this new protocol, they accomplished the first synthesis of the proposed structure of cycloinumakiol **90** and its $C_5$ epimer **91** in a concise fashion (Scheme 58b).[76]

It is not surprising that alkynes can also undergo the intramolecular "cut and sew" reaction with benzocyclobutenones (Scheme 59). Various fused β-naphthols **93** were obtained via isomerization of the initially formed enones **92**. The addition of $ZnCl_2$ co-catalyst was again found to assist forming larger rings (such as **94**, Scheme 60). A decarbonylative alkyne-insertion pathway was achieved by using bulky bidentate ligand DTBM-SEGPHOS in addition to refluxing in xylenes under argon atmosphere.[77] This decarbonylative "cut and sew" reaction offers a unique approach to access fused indene rings (**95**).

Apart from alkene and alkyne insertions, in 2015 the Dong group developed an enantioselective "cut and sew" reaction with more polar C=N bonds. The intramolecular carboacylation of oxime ethers (**96**) with benzocyclobutenones provides an efficient entry to fused tetrahydroisoquinoline rings (Scheme 61).[78] High levels of enantioselectivity were maintained even using substrates as a mixture of *E*/*Z* oxime isomers. Subsequent derivatization of the lactams was possible through *N*-arylation and alkylation upon cleavage of the N–OMe bond (not shown). Saturated tricyclic scaffold **97** was also accessed by hydrogenation of the arene (Scheme 62).

Martin and coworkers realized a highly regioselective intermolecular coupling between benzocyclobutenones and 1,3-dienes or diphenylacetylenes (Scheme 63a).[79] $Ni(COD)_2$ and tri(4-trifluoromethylphenyl)phosphine were found to be most efficient to catalyze insertion of 1,3-dienes to give [4+4] adducts. When $PPh_3$ was used as ligand, the coupling with diphenylacetylene smoothly occurred to give [4+2] products. In all cases, exclusive $C_1$–$C_2$ was observed. While a cyclometalation/β-carbon elimination sequence was proposed in the original work, a recent DFT study supports an oxidative addition-initiated pathway (Scheme 63b).[80]

Recently, Matsuda and coworkers reported an intermolecular coupling between methylidenecyclobutenes (**98**) and alkynes via a pyridine-directed C–C cleavage (Scheme 64).[81] Poly-substituted benzenes were obtained as the final product. For unsymmetrical cyclobutene **99**, olefin isomerization (via **100**) prior to the C–C bond cleavage was proposed to explain the observed two regioisomers **101** and **102**.

### 2.3 Biphenylene

Although TM-mediated activation of biphenylenes has been extensively studied since 1960s, early work mainly focused on either using stoichiometric metals[82] or catalytic cleavage

followed by hydrogenation[83] or dimerization[84]. The first catalytic “cut and sew” reaction with biphenylenes was reported by Jones and coworkers in 1999, where a (dppe)Ni(alkyne) metal complex **103** was found to allow the cycloaddition with acetylene derivatives to generate phenanthrene **104** (Scheme 65a).[85] Under nearly 0.6 mol % $O_2$ atomosphere, the phosphine ligand of **103** is first oxidized to generate the active nickel species, which enables oxidative cyclization with the biphenylenes to form Ni complex **105**. Subsequent migratory insertion and reductive elimination provide the phenanthrene products. Using different Ni precatalysts, C-1 unit insertions were realized with CO and isocyanides, affording fluorenones **106** and fluorine imines **107**. Later, a similar transformation was also achieved by rhodium catalysts (Scheme 65b).[86]

To circumvent the use of $O_2$ to generate the active catalyst, Jones and coworkers prepared a new nickel complex **108** containing a P,N-ligand, which has a higher catalytic performance towards the alkyne-insertion reaction (Scheme 66).[87] In their design, the dissociation of the more labile nitrogen ligand resulted in an open coordination site on the nickel, thus providing a higher reactivity. The combination of a nickel catalyst with a NHC ligand in this transformation was investigated later by the Radius group.[88]

Later in 2008, the Shibata group reported an asymmetric version of this transformation for generating phenanthrene derivatives with axial chirality (**109**, Scheme 67). Employing an iridium catalyst with chiral (*S*, *S*)-Me-BPE ligand **110**, a variety of arylacetylenes were afforded in good yields and moderate to high enantiomeric exces.[89]

Using biphenylene-mediated “cut and sew” reactions to form heteroarenes has also been realized (Scheme 68). The Kotora group reported a rhodium-catalyzed biphenylene-nitrile coupling. Bidentate phosphine ligand was used to give the desired phenanthridines **111** in decent yields.[90]

## 3. Less strained compounds

Clearly, the “cut and sew” transformations with small ring systems are largely driven by strain release. However, significant progress has also been achieved with C–C activation of less strained compounds. The current strategy primarily relies on activation of a polar C–CN bond or employing a DG.

### 3.1 Activation of C–CN bond

C–CN bonds generally possess significantly higher bond dissociation energy (>100 kcal/mol) than C–C single bonds (around 85 kcal/mol). However, due to their strong electron-withdrawing nature and high binding affinity with TM of the CN moiety, the polar C–CN bonds are prone to undergo oxidative addition with TMs.[91] Hence, catalytic C–CN bond activation is feasible and has been extensively studied. In particular, carbocyanation of an unsaturated π moiety via C–CN bond activation provides a unique approach to prepare nitrile compounds.[92] Since the early work of intermolecular coupling between arylnitriles and internal acetylenes by Hiyama and Nakao in 2004,[93] a variety of nitrile derivatives, such as allylnitriles,[94] carbonocyanidates,[95] carbamoyl cyanides,[96] alkynylnitriles, and alkenylnitriles were demonstrated to be well compatible for such a “cut and sew”

transformation. In addition, the carbocyanation reaction also proceeded in an intramolecular fashion,[93b,96a–b,97] where use of chiral ligands provided the cyclization products with high enantioselectivities.[96c,98] Acyl nitriles[99] and α-iminonitriles[100] have also been employed as the coupling partners, leading to more functionalized nitrile products. Importantly, Lewis acids, such as $BPh_3$, $AlMe_3$ and $AlMe_2Cl$, were demonstrated in 2007 by Hiyama and Nakao to greatly increase the reactivity of the carbocyanation reactions,[101] presumably through coordination with the cyano group to facilitate the oxidative addition step. Similarly, the incorporation of a Lewis acid co-catalyst also enabled reactions with challenging substrates such as alkenylnitriles, alkynylnitriles[101,102] and alkylnitriles[101, 103].

Generally, the reaction initiates from the complexation between a TM and a nitrile substrate, followed by oxidative addition into the C–CN bond (Scheme 69). The resulting alkyl/aryl/acyl–metal bond then undergoes migratory insertion into the unsaturated unit, such as alkenes, alkynes and allenes,[104] followed by subsequent C–CN bond-forming reductive elimination to furnish the “cut and sew” product **114**. Given that this area has recently been extensively reviewed by Nakao[92b–c, 105], Chatani[106], and others[92a,d,f,107], detailed discussions will not be included in this perspective.

### 3.2 Use of a Directing group

One important strategy to activate unstrained C–C bonds is employing an intramolecular coordinating group to deliver a TM to insert into a particular C–C bond.[108] Such a directing strategy generally lowers the kinetic barrier for the oxidative addition step, and often forms a five-membered metallacycle as the key intermediate. In 1981, Suggs and Cox reported the first directed C–C activation of a linear ketone using a quinoline moiety as the DG.[109] However, the corresponding “cut and sew” transformation with the 8-acylquinoline system did not appear until the Douglas’ work in 2009.[110] Using alkene-tethered substrate **115**, they achieved an intramolecular carboacylation via directed C–C cleavage of the acyl–aryl bond (Scheme 70). A variety of 1,1-disubstituted alkenes were used, providing products **116** bearing quaternary carbon centers in good yields, while mono-substituted alkenes gave low yields likely caused by a β-hydrogen elimination pathway. Mechanistic studies by Johnson and coworkers[111] revealed that for substrates with a less-hindered alkene, the oxidative addition is the rate-determining step in this transformation; whereas larger substituents on the alkene or substrates with longer tethers decelerated the migratory insertion step, rendering it the rate-determining step (Scheme 71).

Shortly after, the transformation was extended to an intermolecular carboacylation with norbornene derivatives (Scheme 72).[112] To minimize the undesired C–H activation pathway, the Douglas group employed a cationic rhodium precatalyst with a triflate counterion in a more polar solvent such as THF. This condition favors the “cut and sew” transformation providing the insertion products in moderate yields.

In 2015, Zeng and Dong reported a directed C–C activation of isatin derivatives (**117**),[113] in which one equivalent of CO was removed from the substrate followed by alkyne insertion to provide various 2-quinolinones (Scheme 73). The overall reaction is considered as a [5+2–1] transformation. To circumvent the undesired ortho C–H activation, 3-methylpyridyl group was found to be effective by controlling the orientation of the metal. Alkynes bearing a

myriad of functional groups, such as unprotected alcohols, esters and ketones were tolerated. Unsymmetrical internal alkynes provide high regioselectivity with larger substituents at the 4-position (e.g. **118**). Terminal alkynes, though tolerated, gave moderate yields and regioselectivity (e.g. **119**). Mechanistic exploration shows that the Rh insertion into the C–C bond can occur at room temperature; however, migratory insertion of alkynes did not happen below 130 °C.

Very recently, the Dong group developed an intermolecular isatin/isocyanates coupling reaction through a double decarbonylation pathway (Scheme 74).[114] Use of electron-deficient ligands such as $AsPh_3$ proved crucial to provide the benzimidazolidinone products **120** in excellent yields. A range of functional groups were found compatible. Use of *in situ* generated isocyanates from the corresponding acyl azides was also efficient (such as in products **121** and **122**). Interestingly, an isotope labelling study using the $^{13}C$-labeled isocyanate revealed both the carbonyl groups from the isatin starting material were removed during the reaction (Scheme 75).

## Conclusion and Outlook

Taking advantage of C–C activation as a unique mode of reactivity, a large variety of “cut and sew” transformations has been developed. These reactions either provide unusual bond disconnection strategies to access known systems, or afford novel scaffolds that are challenging to be prepared using conventional approaches. These transformations are typically pH and redox neutral, and highly atom economical. Consequently, the functional group tolerance is generally excellent. It is expected that with a better understanding of the mechanism of the TM-mediated C–C activation processes, more efficient catalyst systems (e.g. catalysts with high TONs and TOFs) and milder reaction conditions, such as lower reaction temperature, will be developed in the future. While the majority of current methods employ strained substrates to gain thermodynamic driving forces, participation of less strained systems recently started to grow. However, general “cut and sew” transformations with less or non-stained substrates are rare and typically require use of a permeant directing moiety, except the C–CN bond activation methods. It is envisioned that more synthetically useful transformations or new C–C activation modes with less strained systems might become an interesting research direction in the near future.

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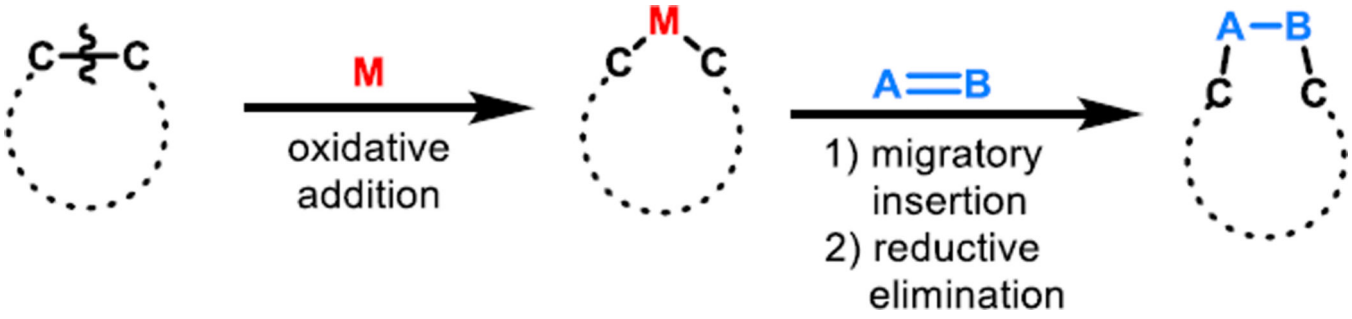
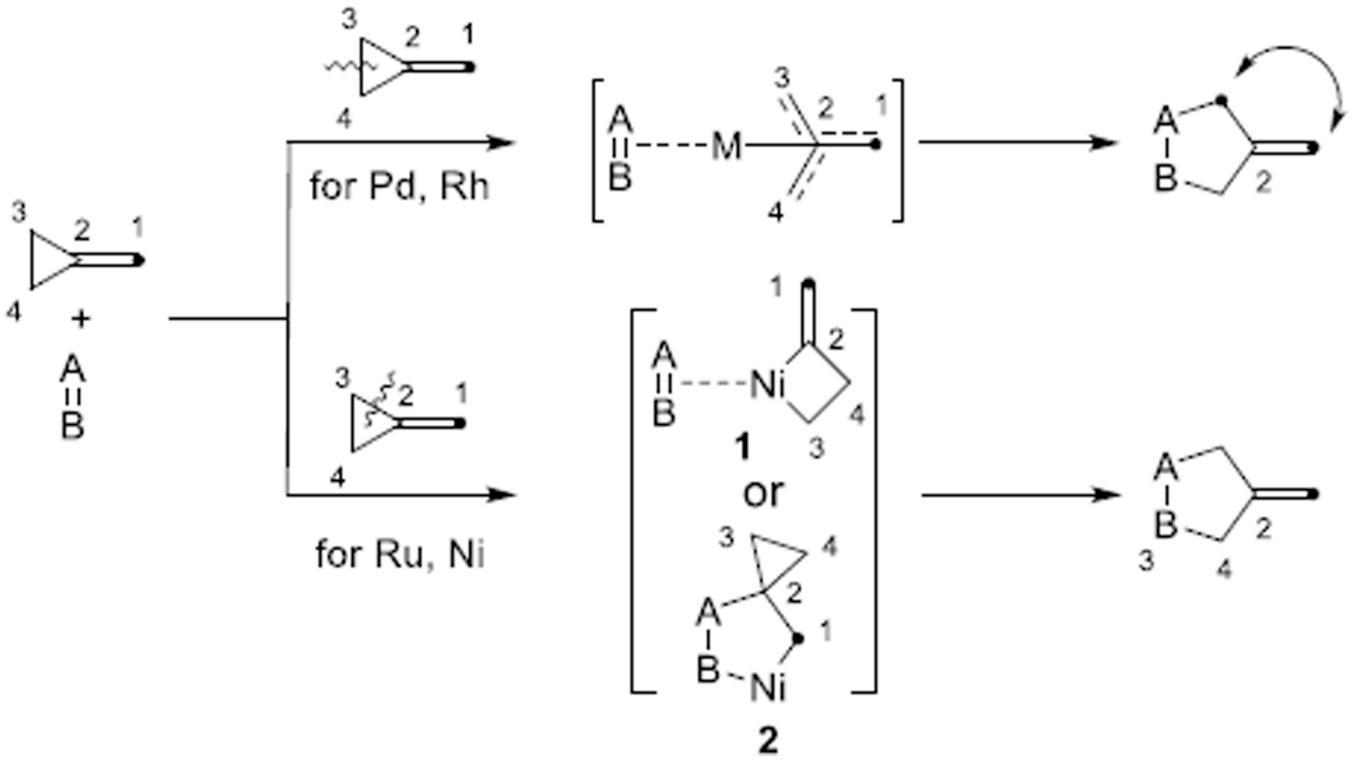
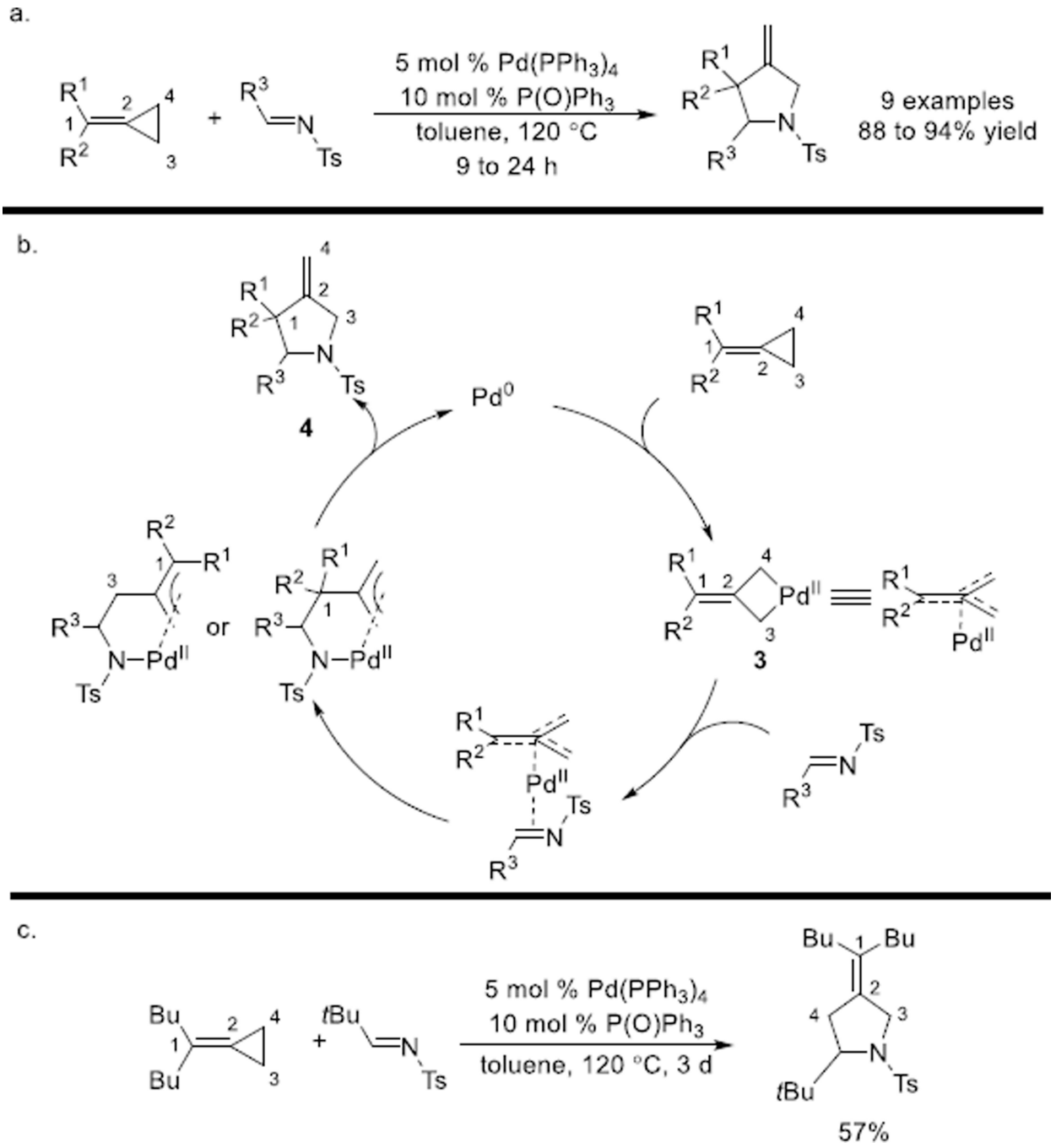


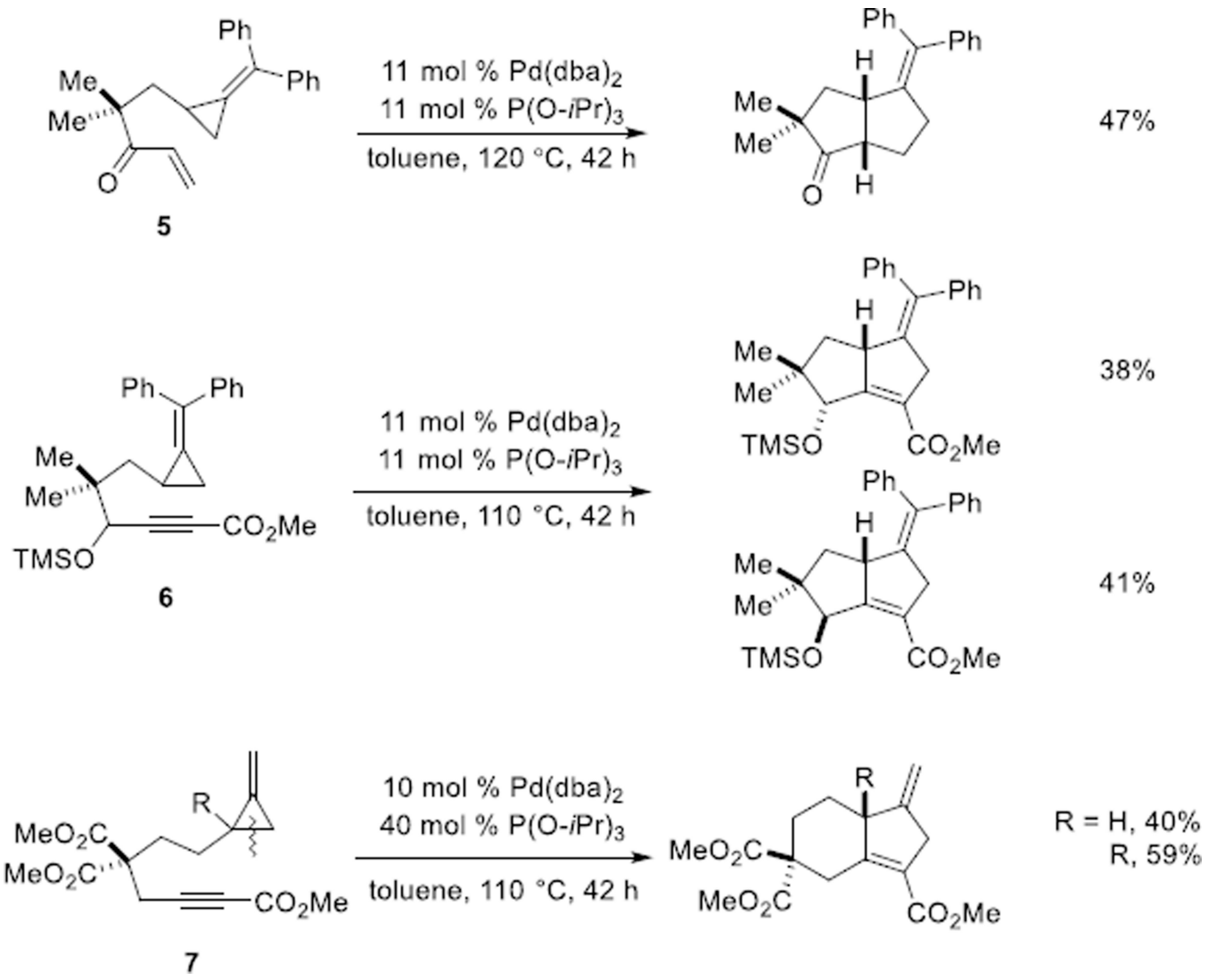

**Scheme 1.**
"Cut and sew" transformations




**Scheme 2.**
Reaction patterns for ACPs

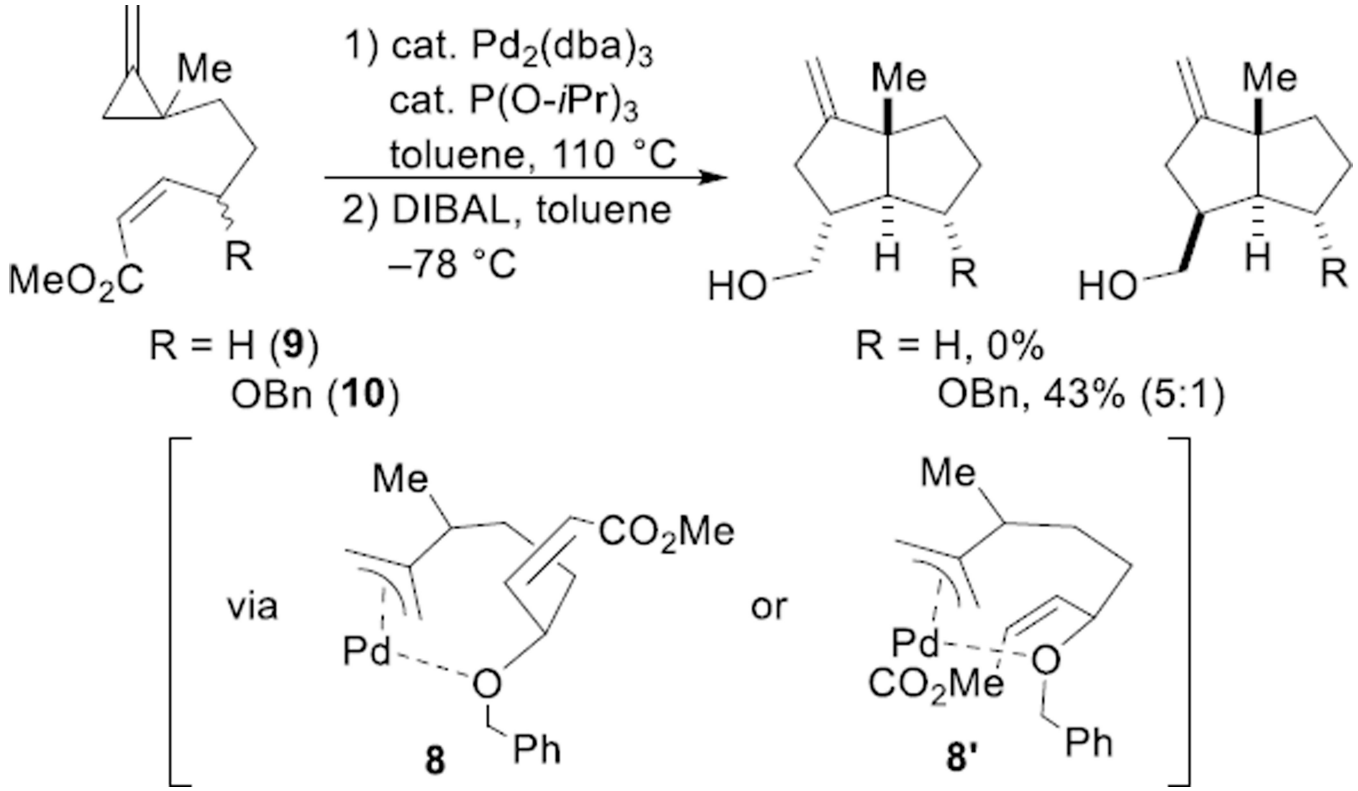



**Scheme 3.**
Substitution-controlled [3+2] cycloaddition of ACPs

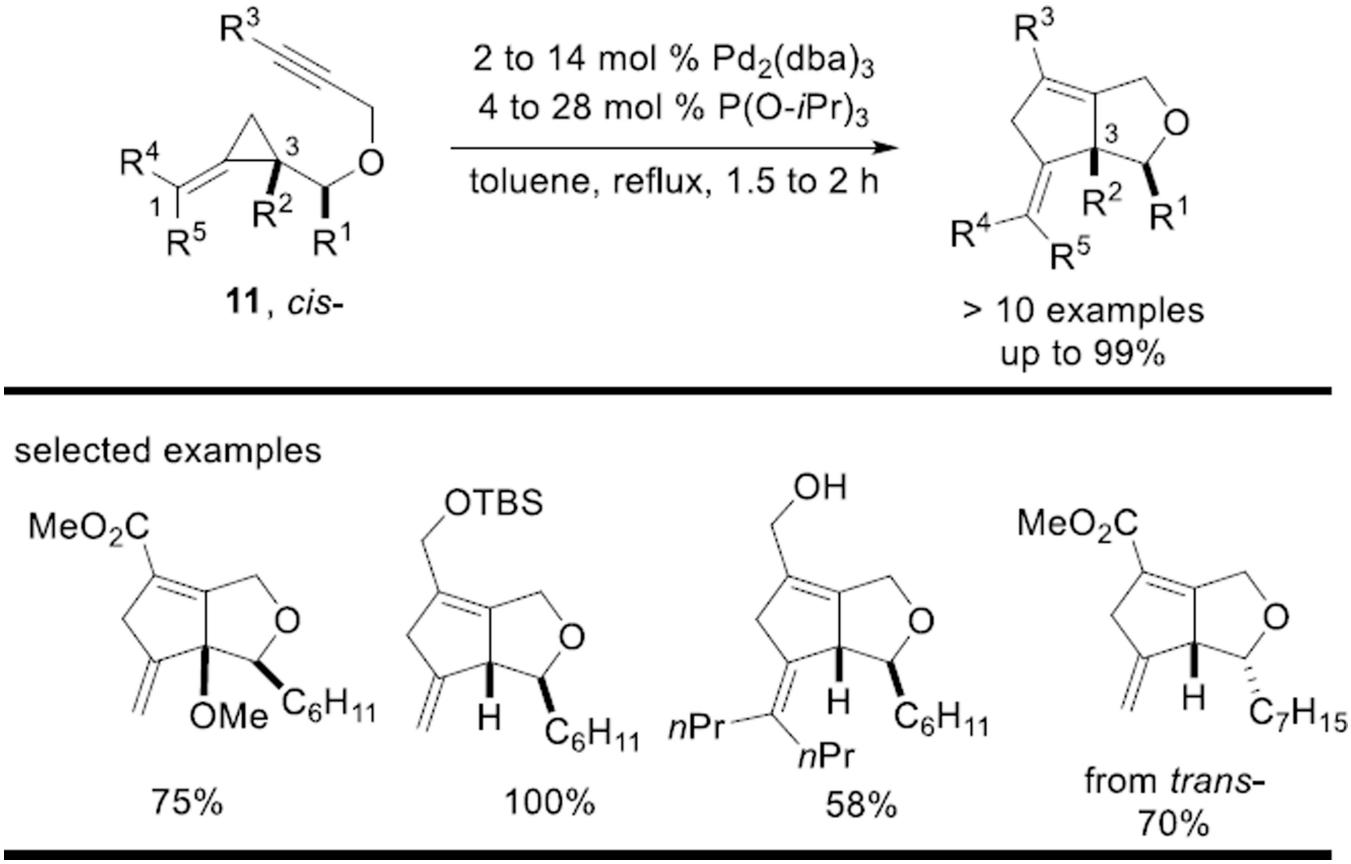



**Scheme 4.**

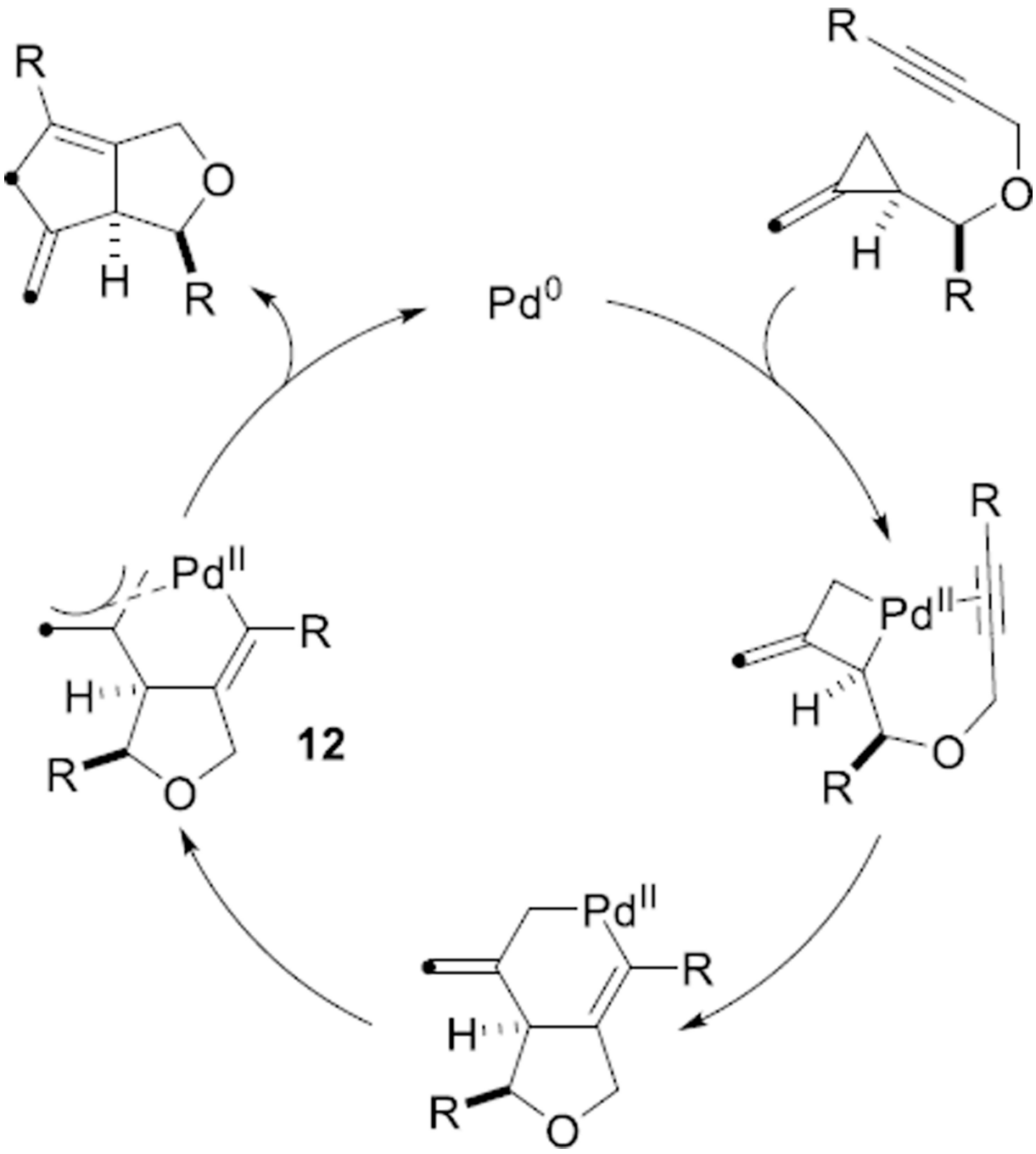
Pd-catalyzed intramolecular cycloaddition between ACPs and alkenes or alkynes



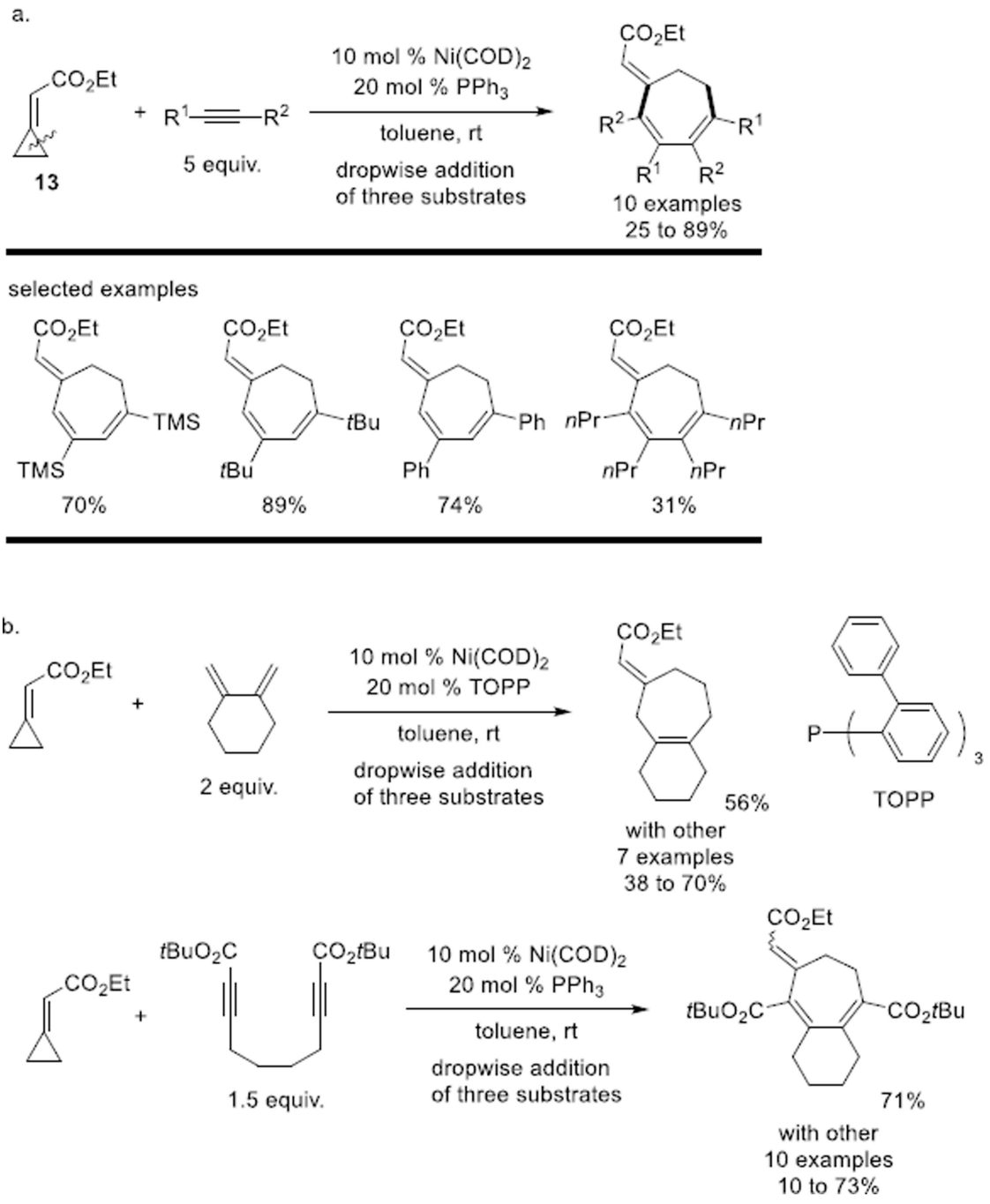

**Scheme 5.**
Heteroatom-assisted intramolecular cycloaddition between simple MCPs and alkenes




**Scheme 6.**
Stereoselective intramolecular [3+2] reactions of ACPs with tethered alkynes

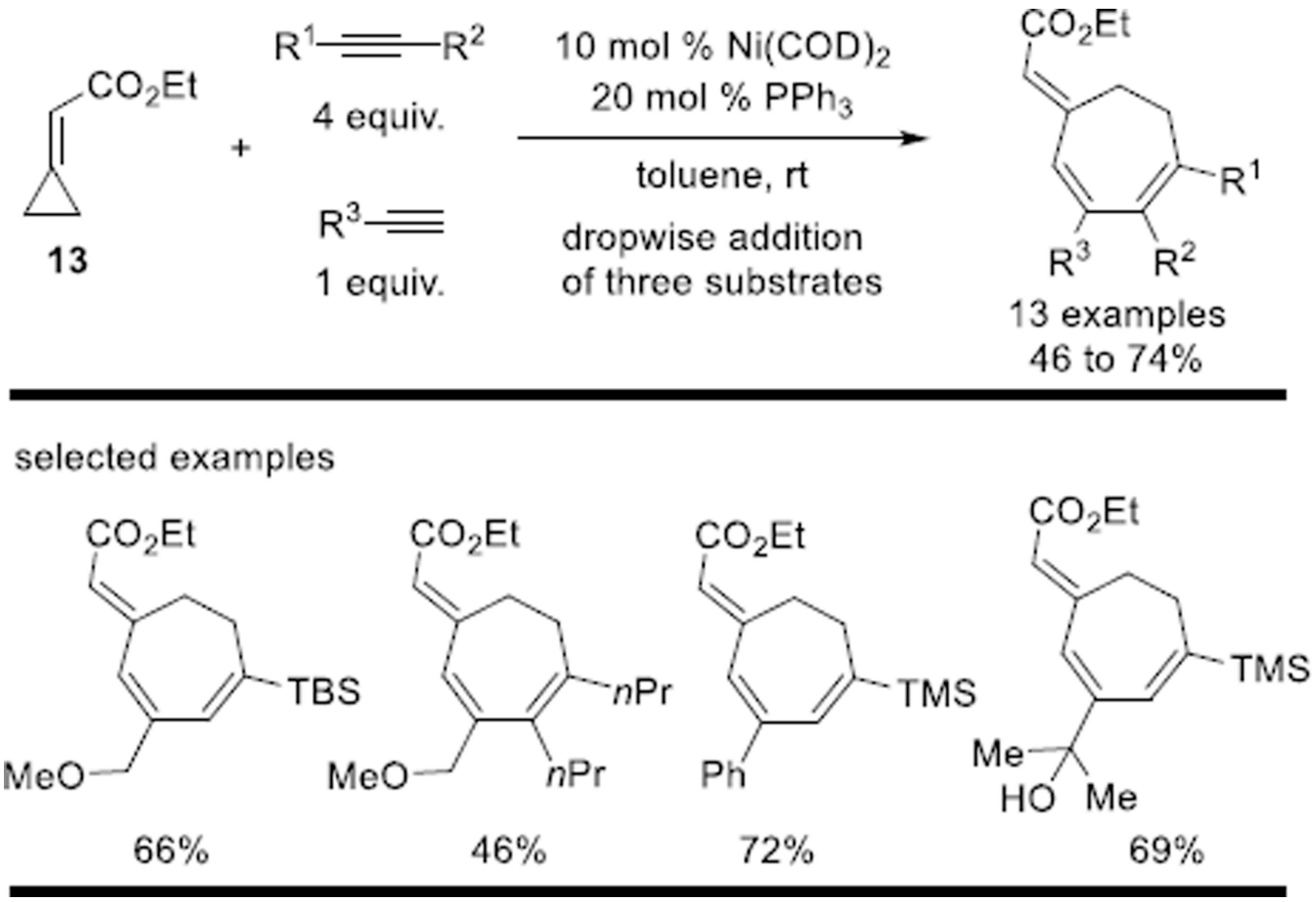



**Scheme 7.**
Proposed mechanism for the intramolecular [3+2] reactions of ACPs with tethered alkynes

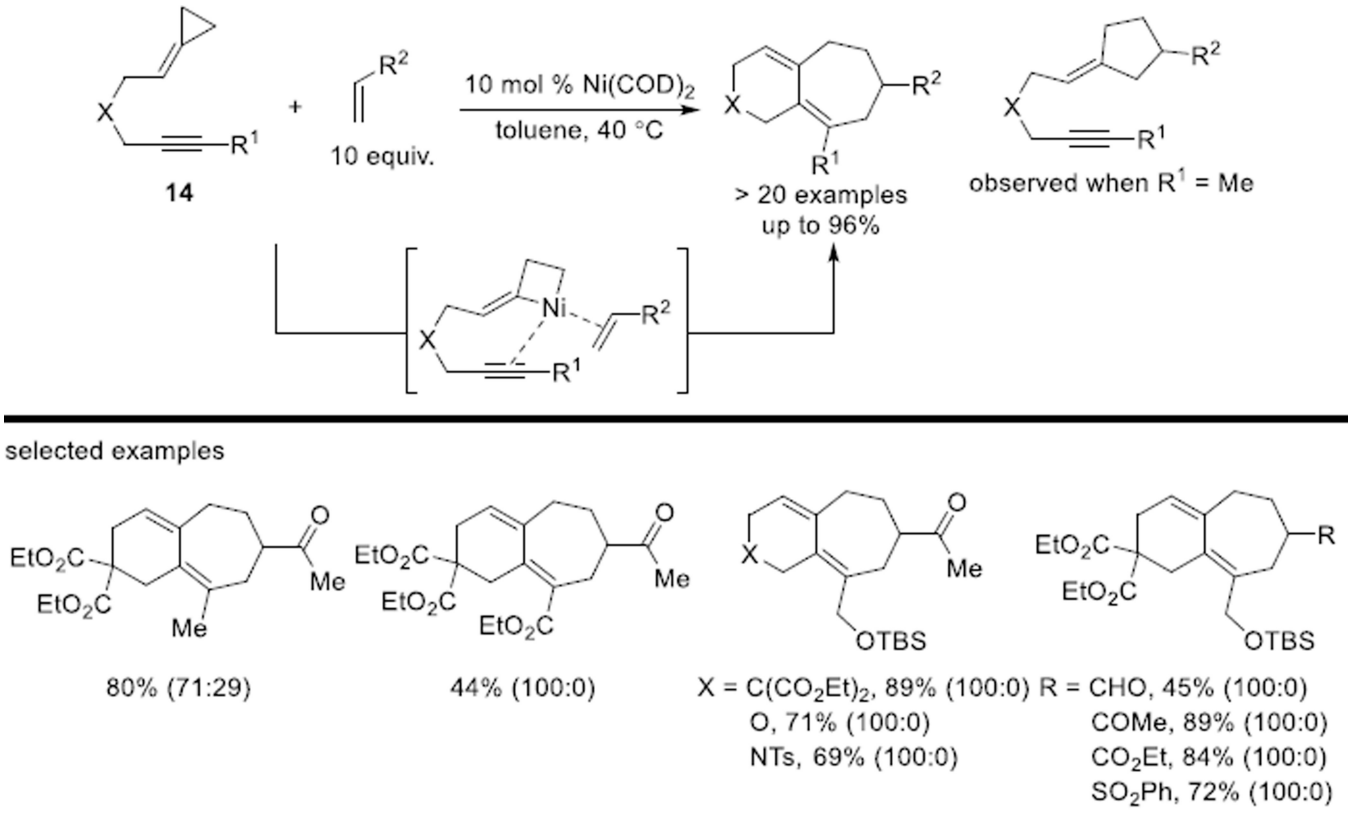



**Scheme 8.**

Ni-catalyzed intermolecular cycloaddition with cyclopropylideneacetates

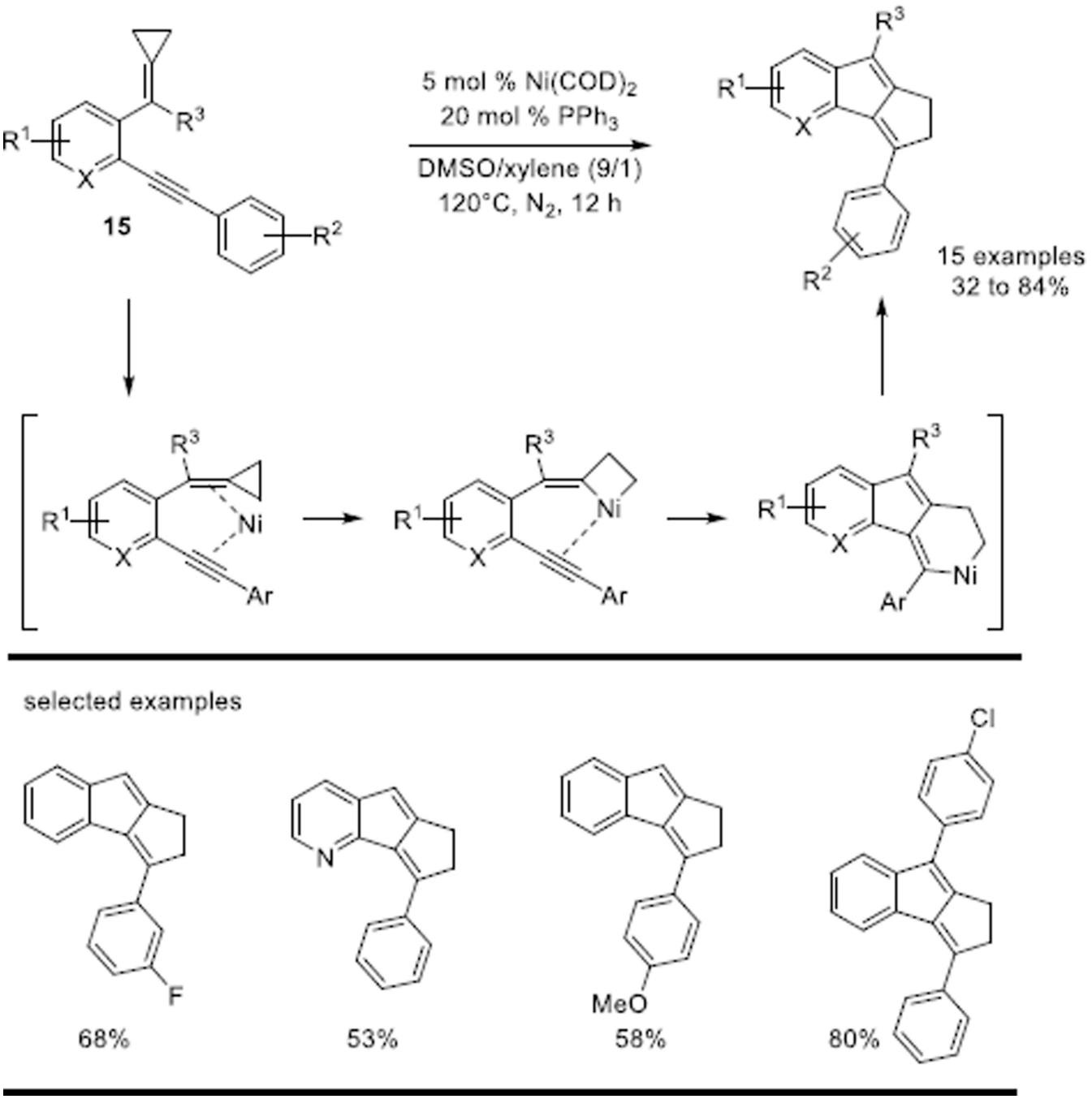



**Scheme 9.**
Ni-catalyzed intermolecular [3+2+2] cycloaddition with two different alkyne components

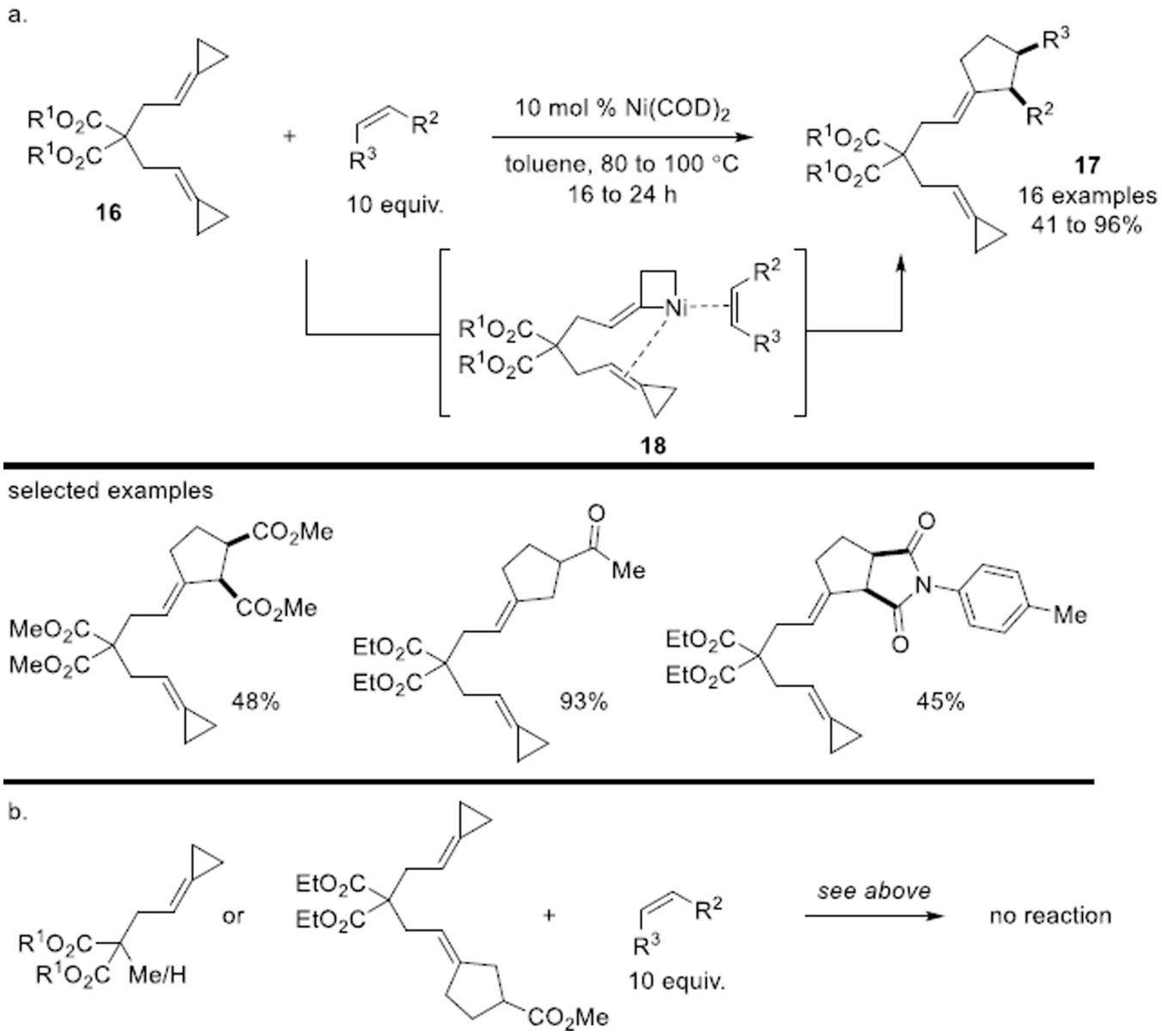



**Scheme 10.**

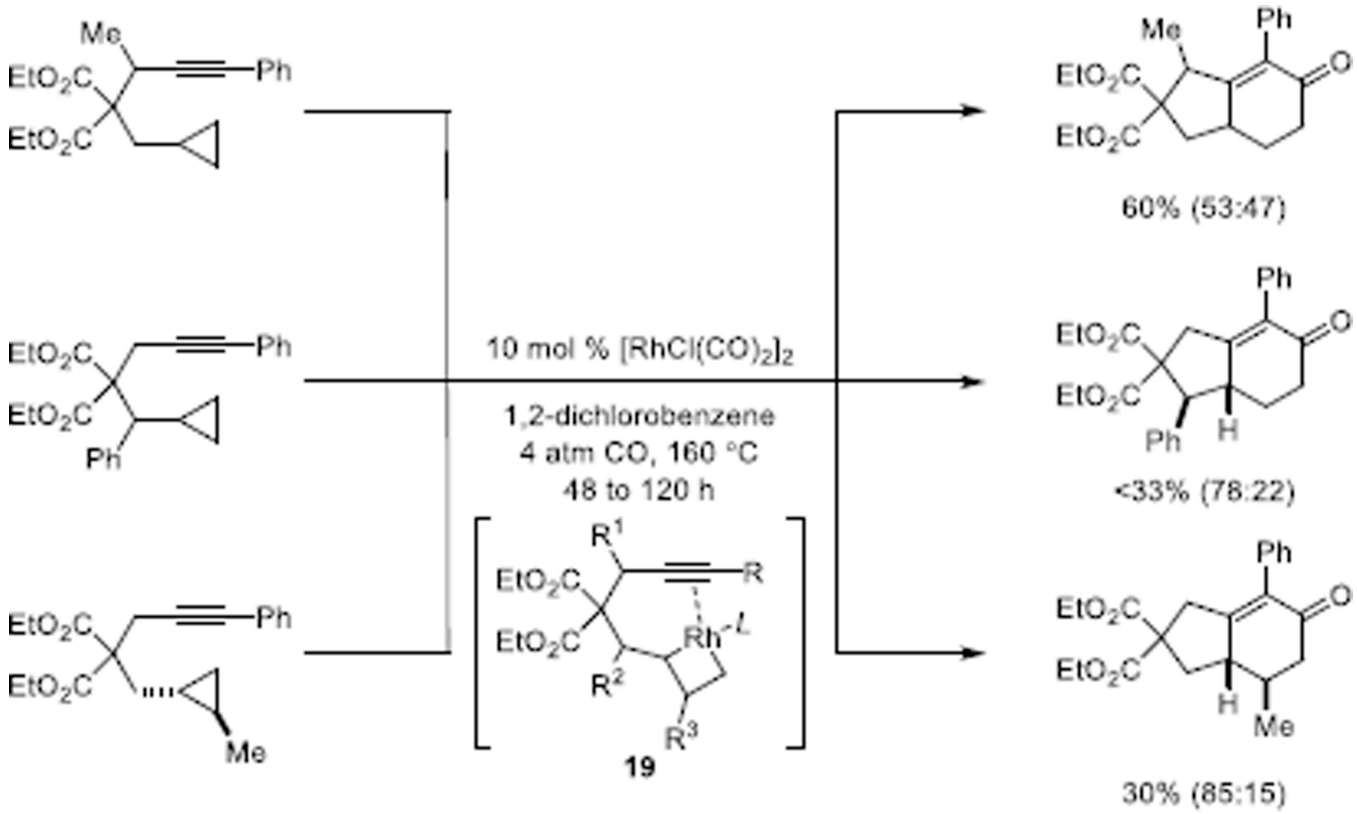
Ni-catalyzed [3+2+2] cycloadditions between alkyne-tethered ACPs and alkenes




**Scheme 11.**
Ni-catalyzed cycloaddition of ACPs and alkynes via proximal C–C cleavage

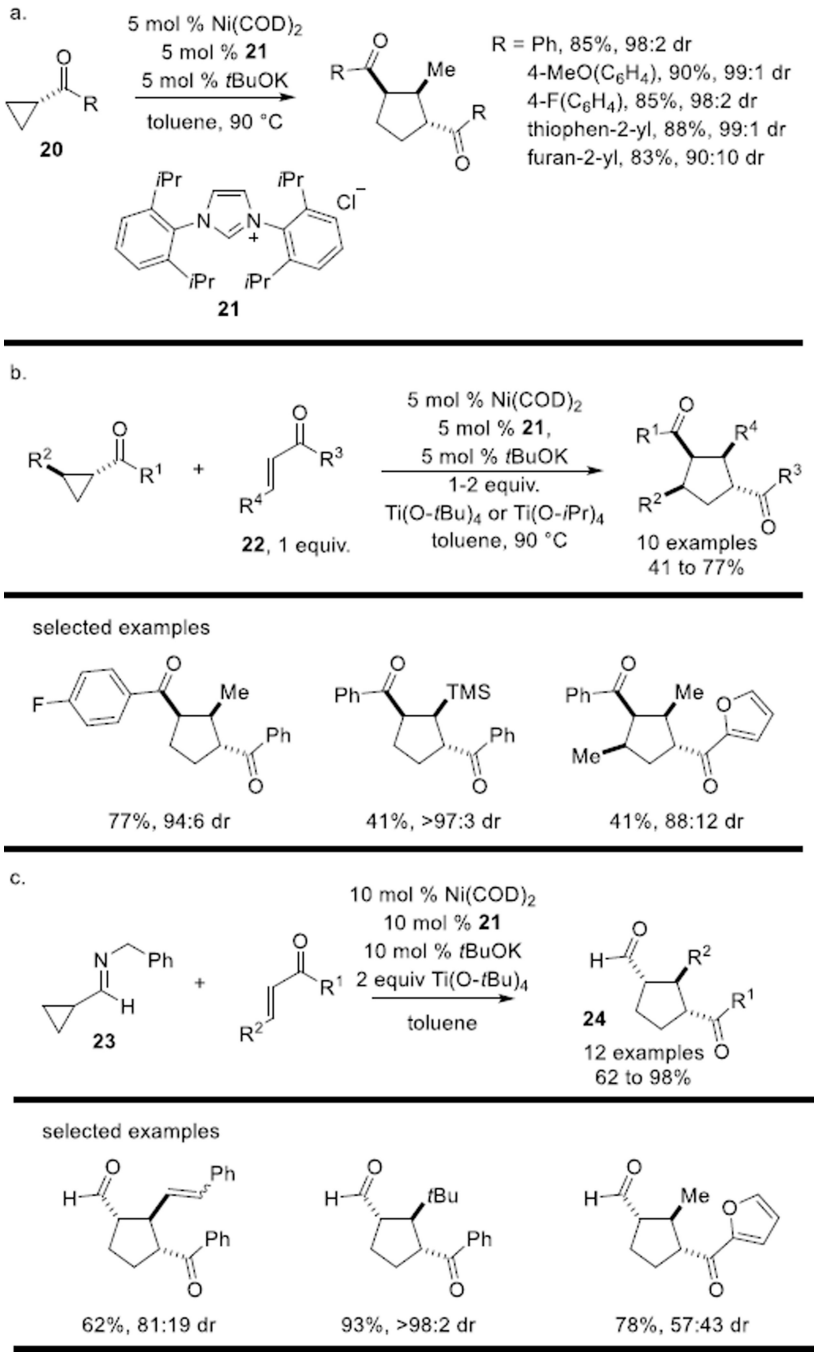



**Scheme 12.**
Alkene-assisted intermolecular [3+2] cycloaddition of ACPs and alkenes



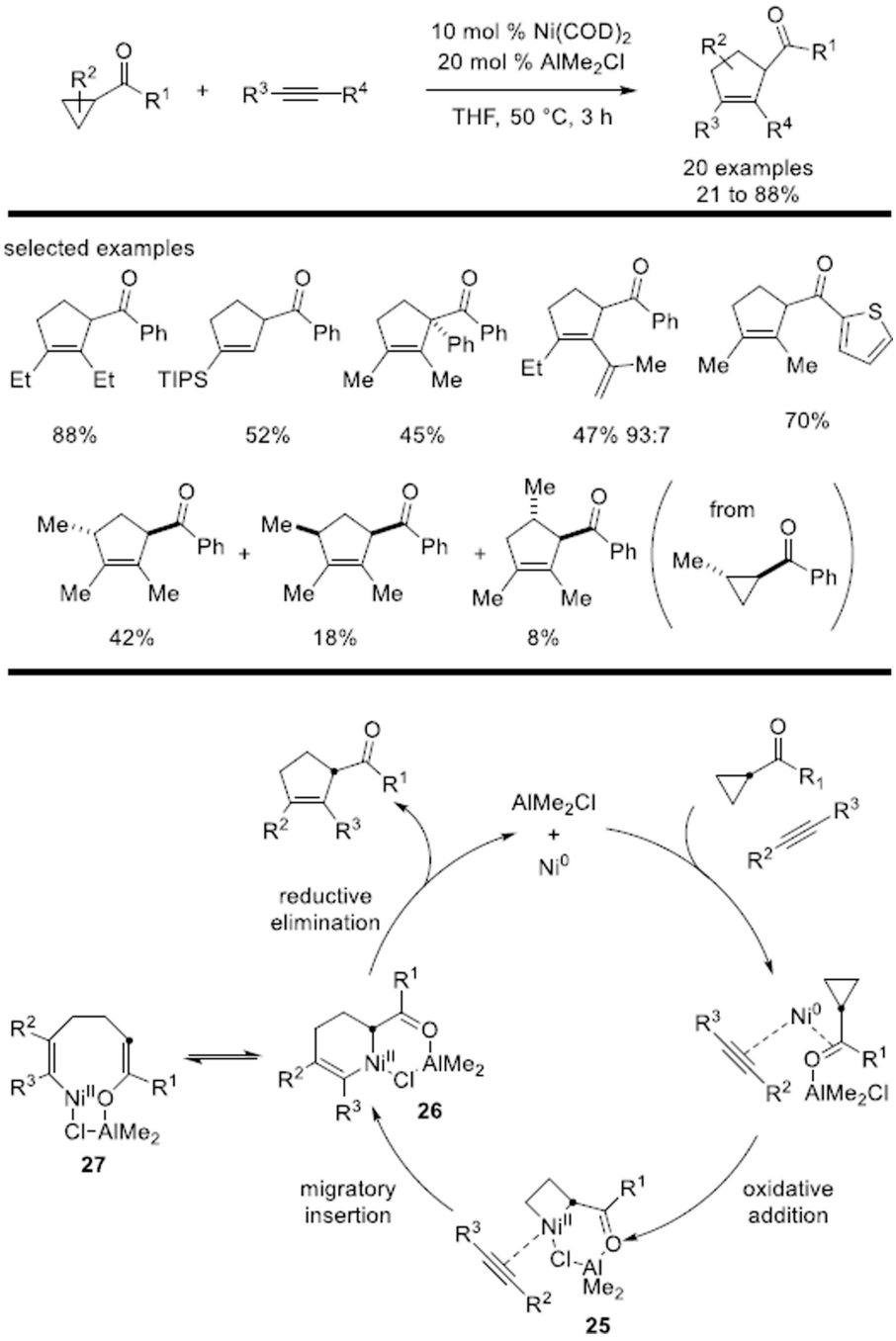

**Scheme 13.**

Rh-catalyzed intramolecular [3+2+1] cycloaddition of simple cyclopropanes with alkynes



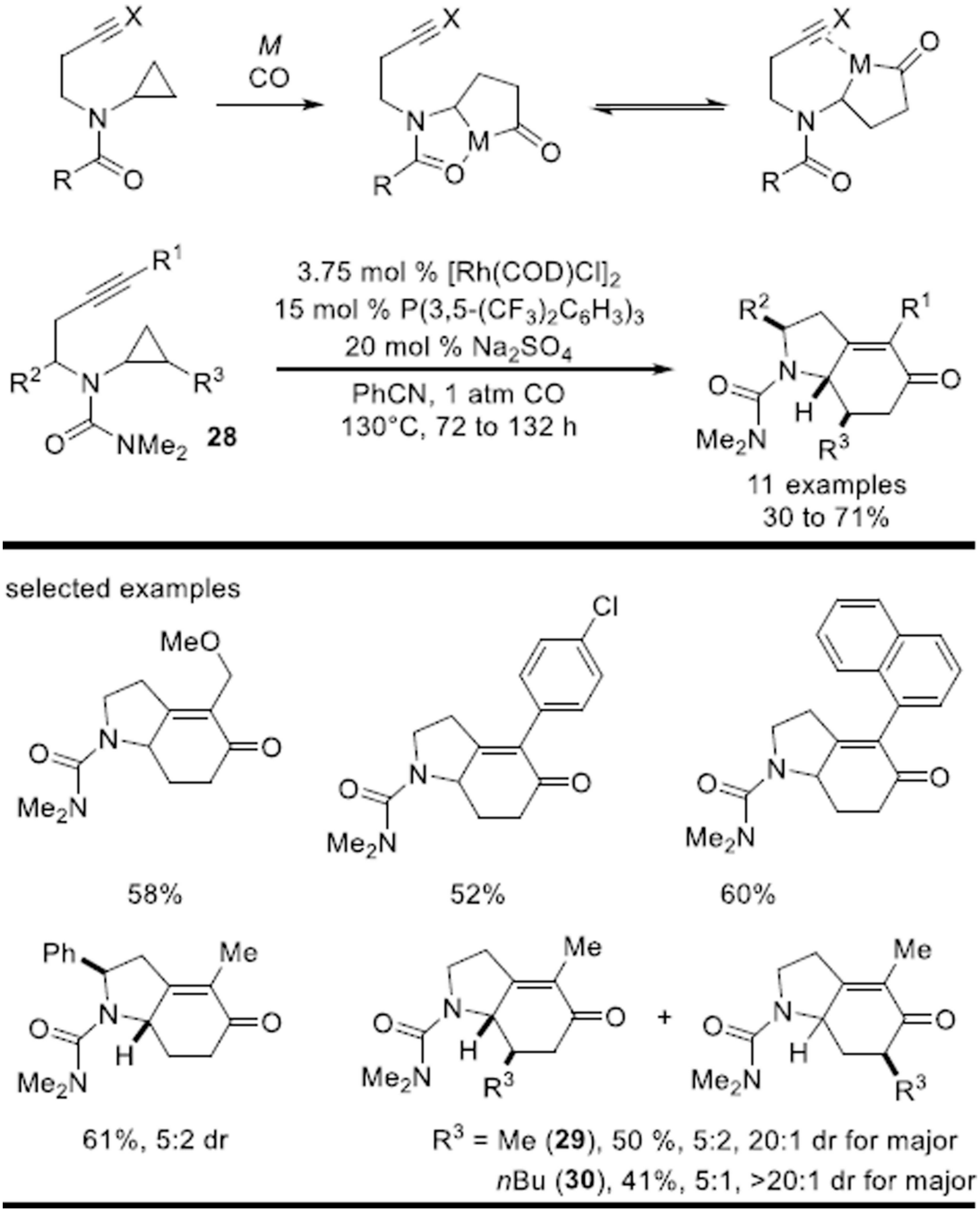

**Scheme 14.**

Ni-catalyzed intermolecular [3+2] cycloaddition of acyl cyclopropanes with enones



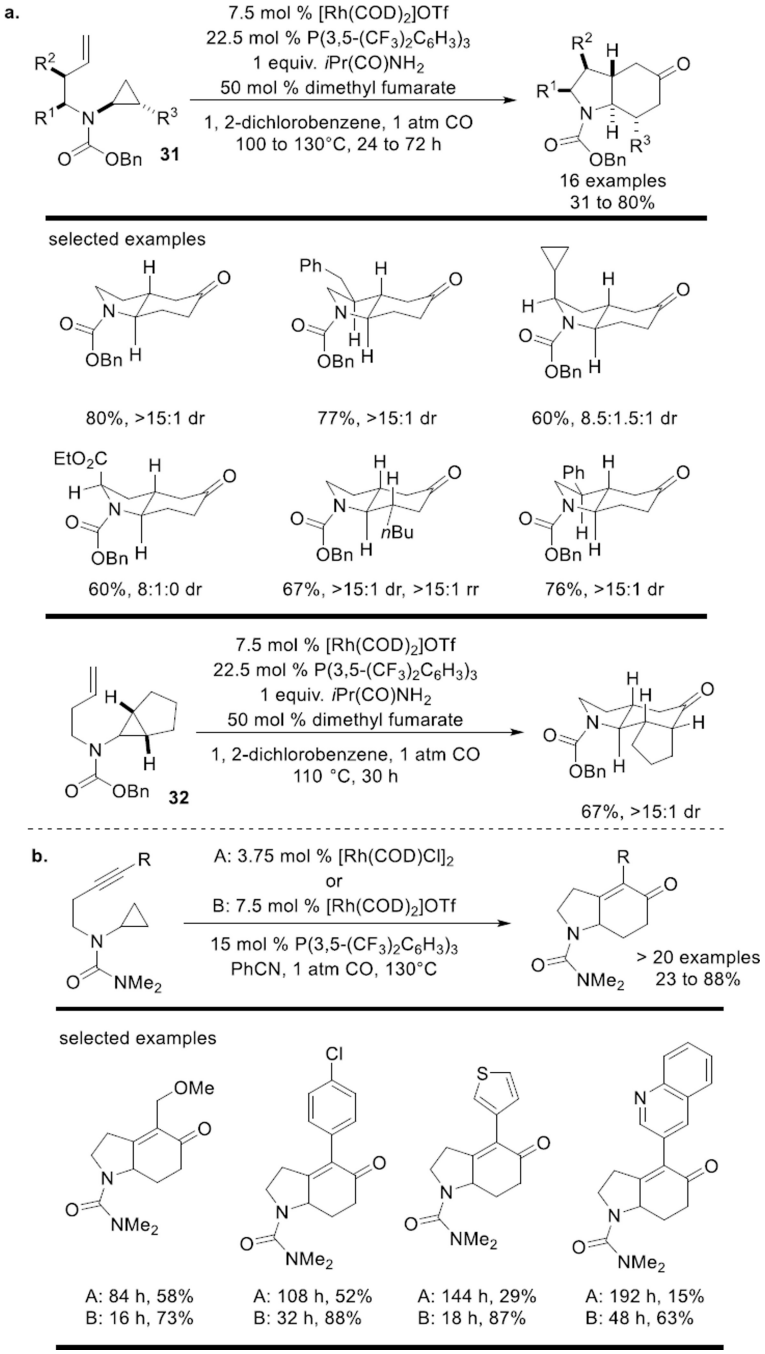

**Scheme 15.**

Ni-catalyzed intermolecular [3+2] cycloaddition of cyclopropyl ketones with alkynes



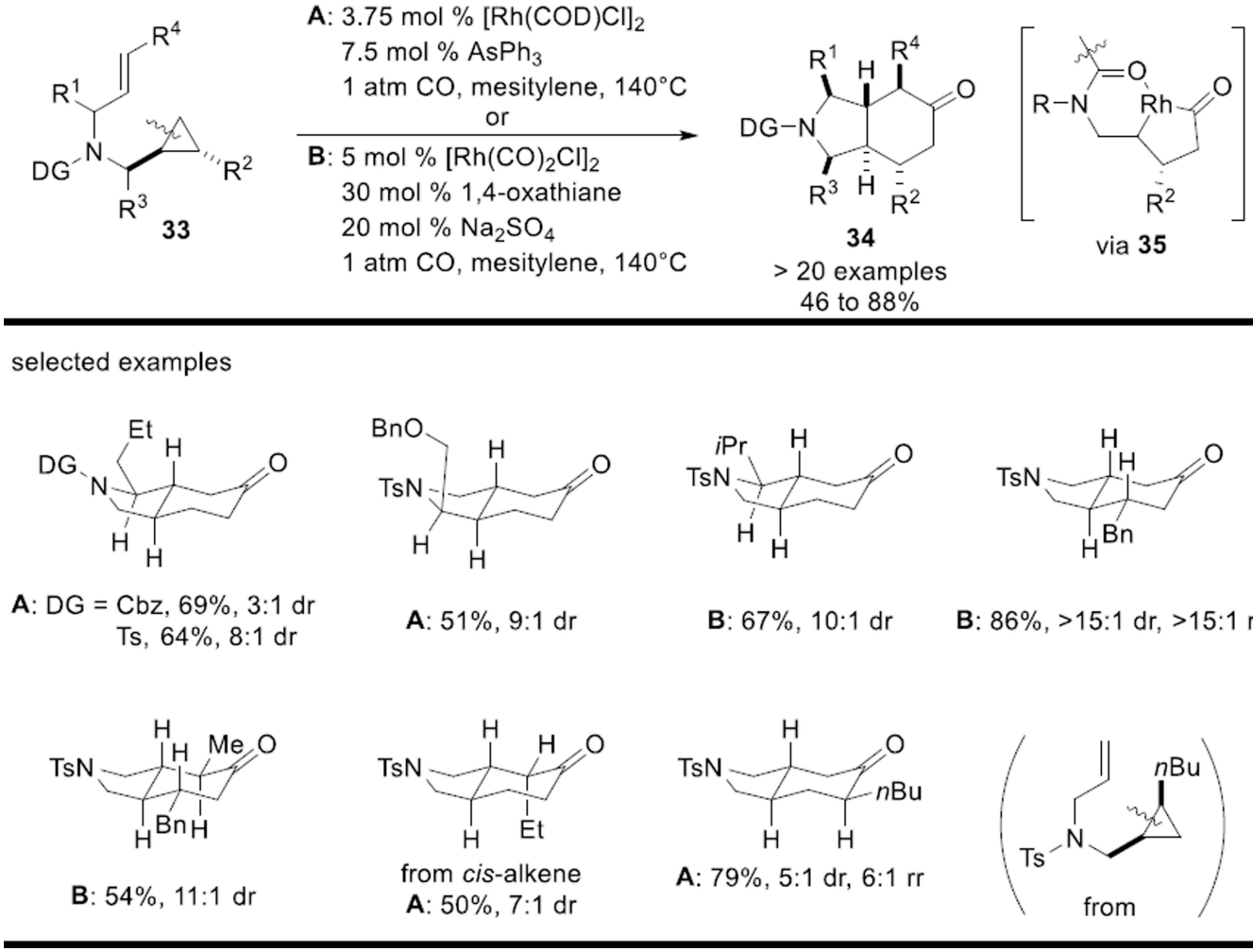

**Scheme 16.**

Urea-directed Rh-catalyzed intramolecular [3+2+1] cycloaddition of cyclopropyl amides with alkynes



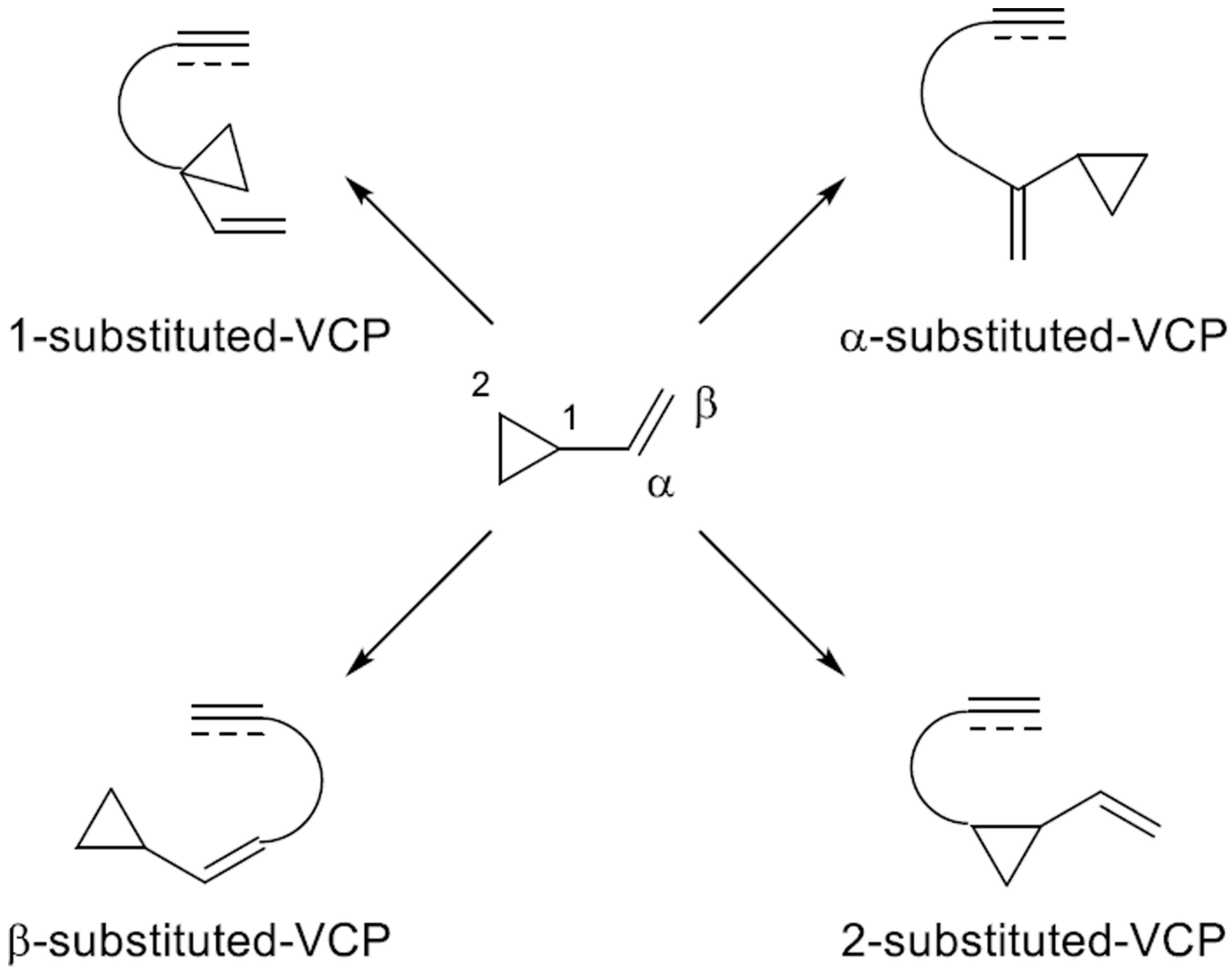

**Scheme 17.**

Cationic rhodium-catalyzed for [3+2+1] cycloaddition of cyclopropyl amides

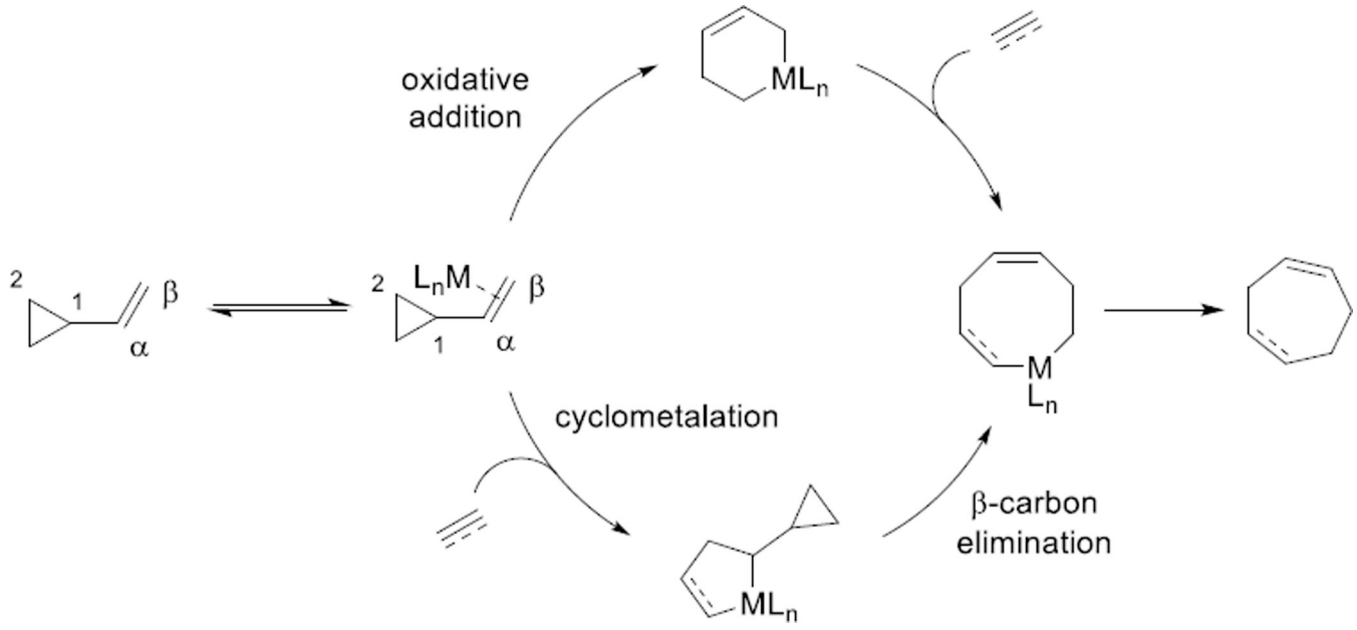



**Scheme 18.**

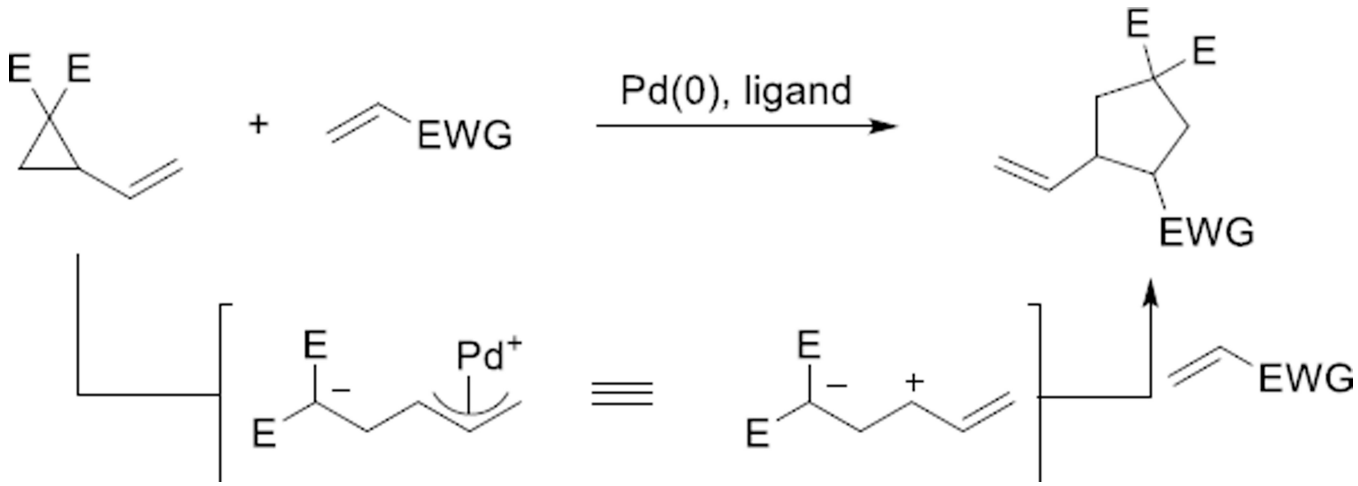
Directed intramolecular [3+2+1] cycloaddition of aminomethylcyclopropanes



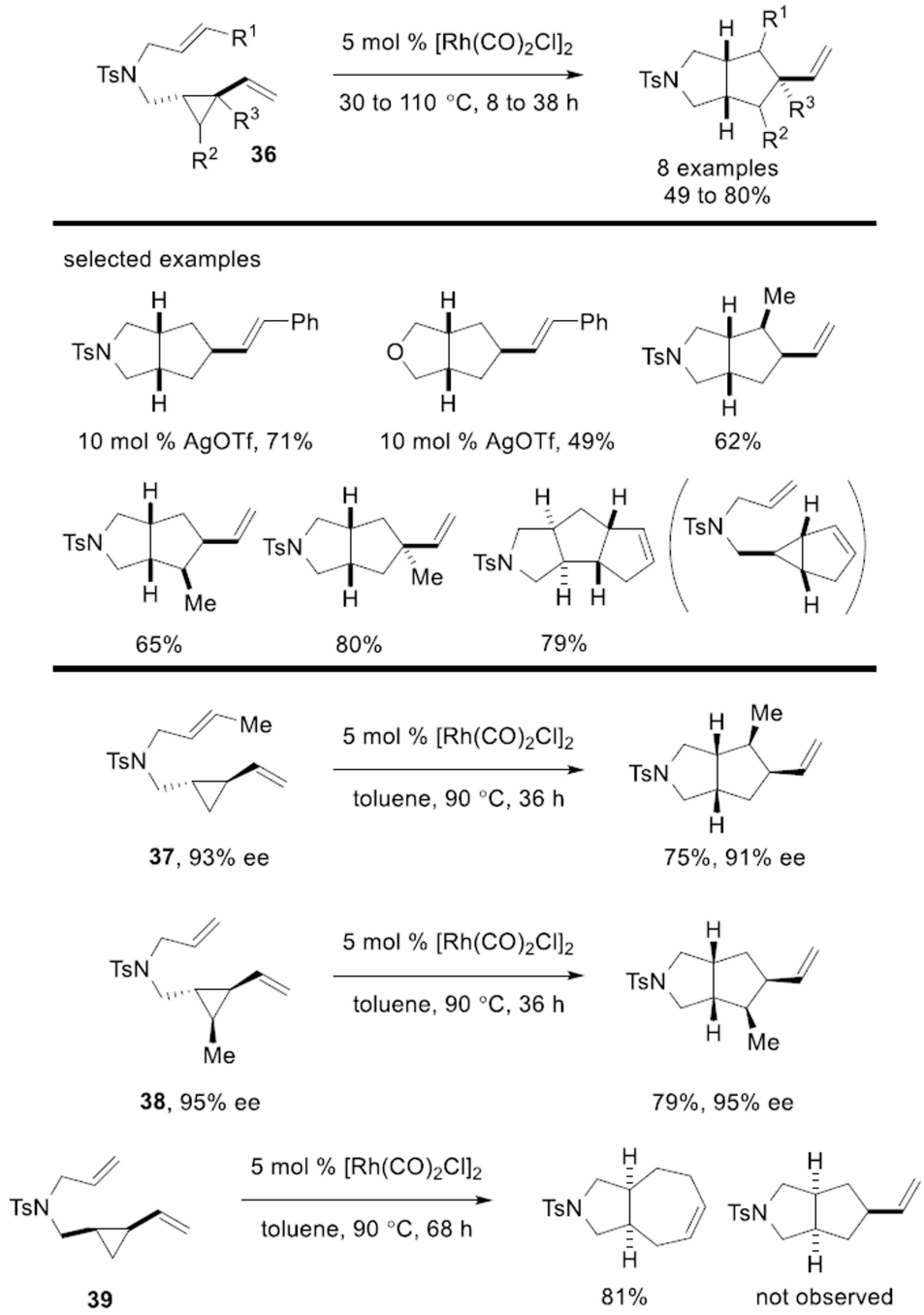

**Scheme 19.**
General types of VCPs



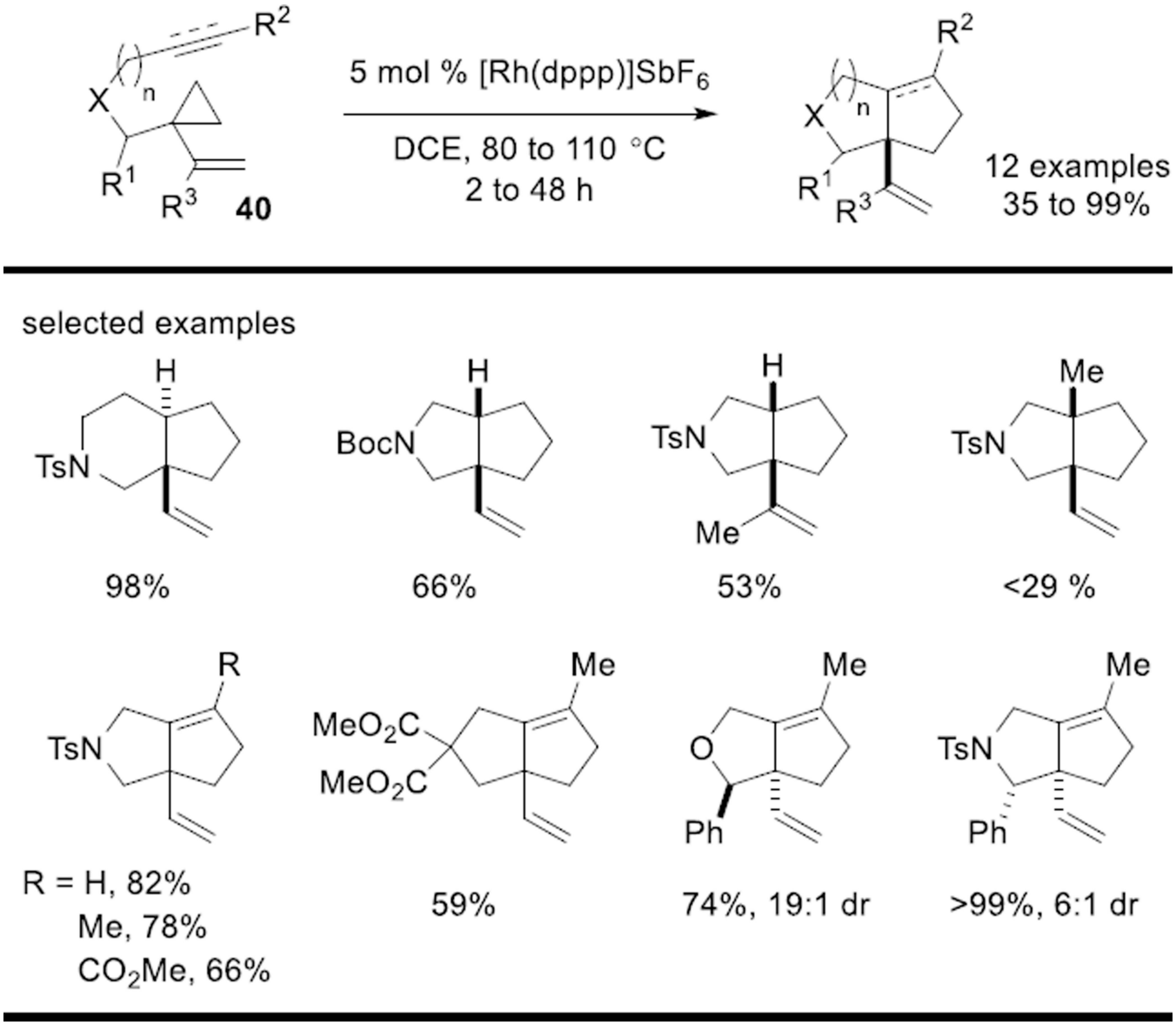

**Scheme 20.**
Two mechanistic pathways for VCPs acting as a five-carbon component



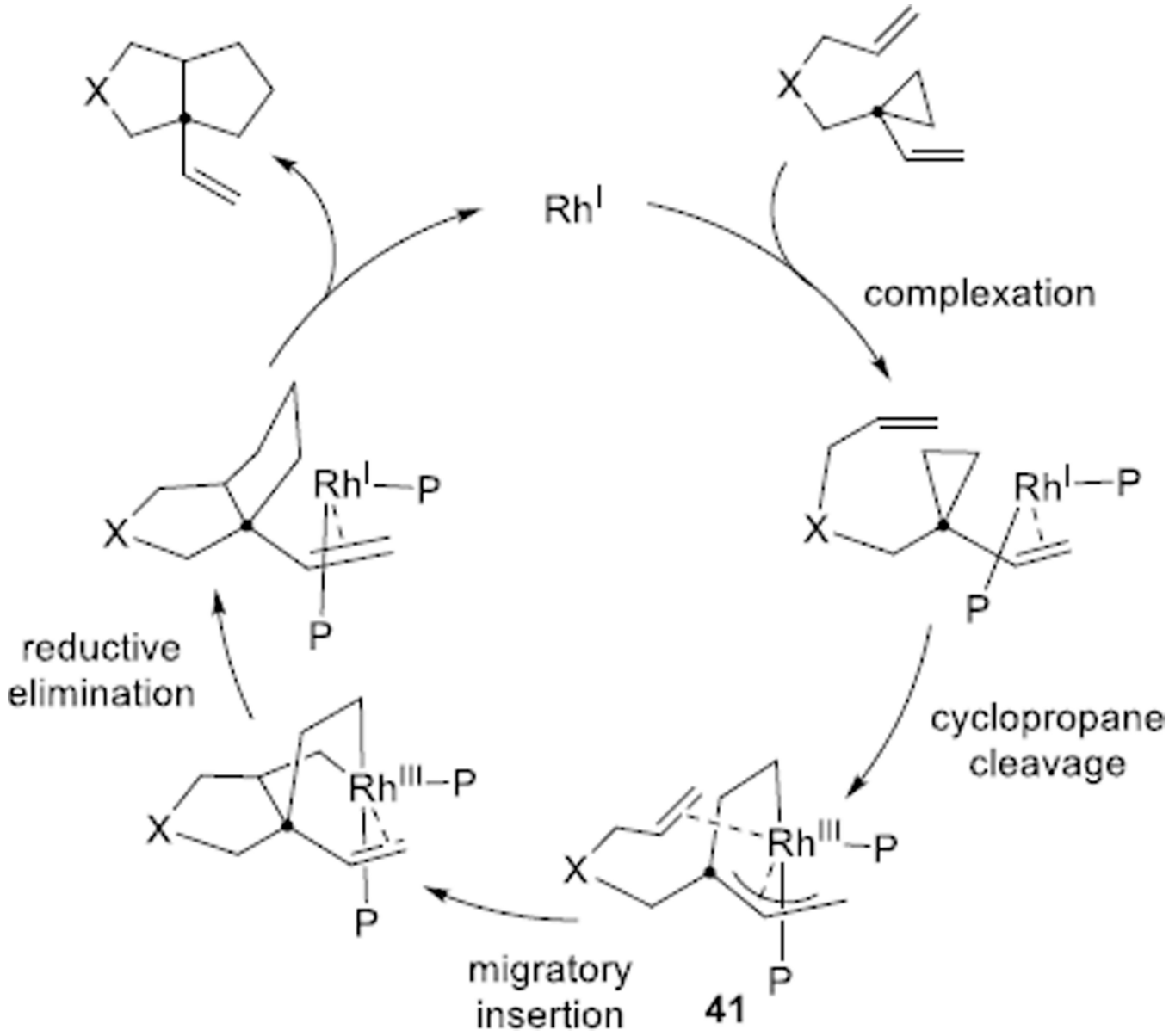

**Scheme 21.**
VCPs serving as 1,3-dipoles



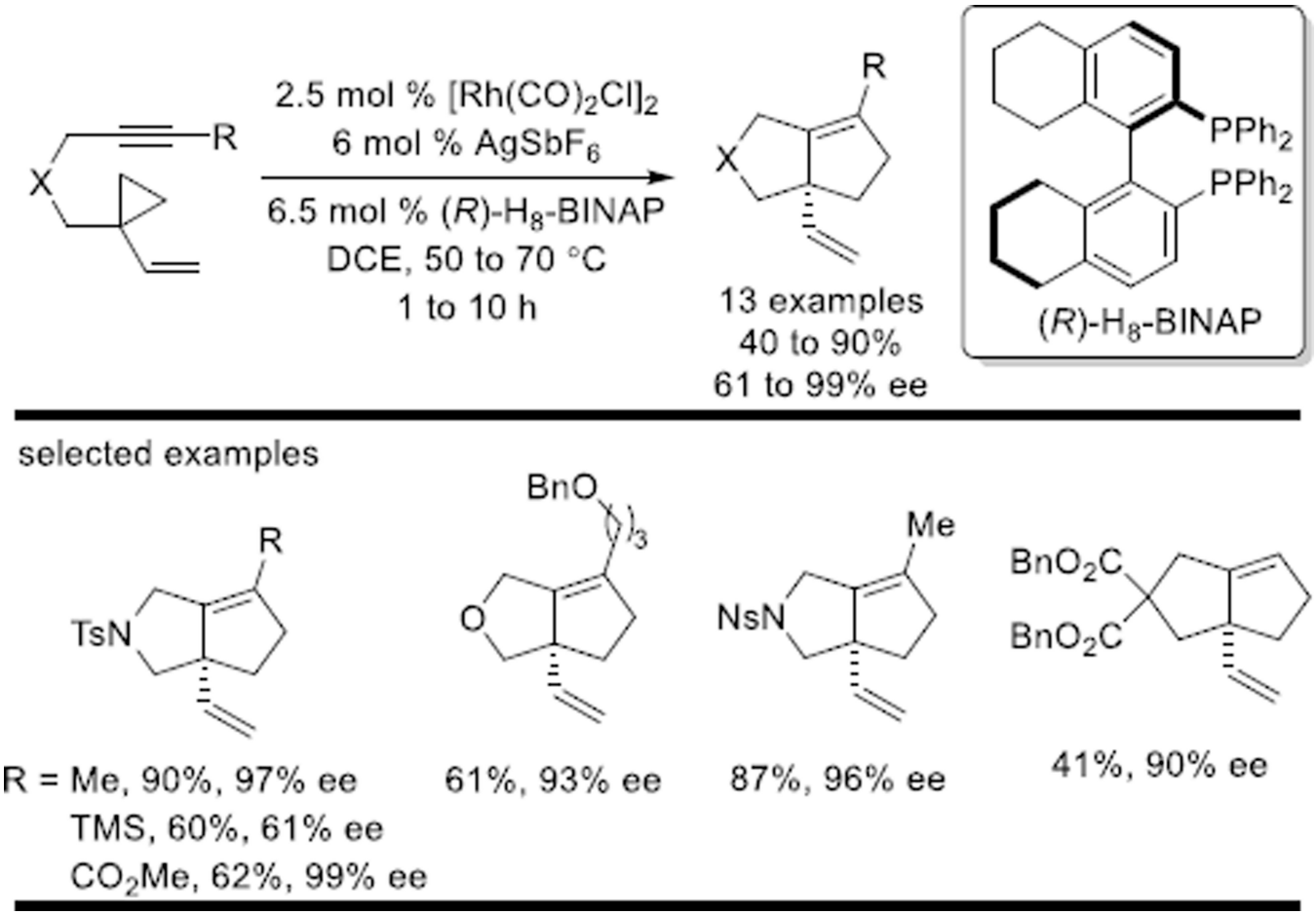

**Scheme 22.**
Rh-catalyzed [3+2] cycloaddition of 2-ene-VCPs



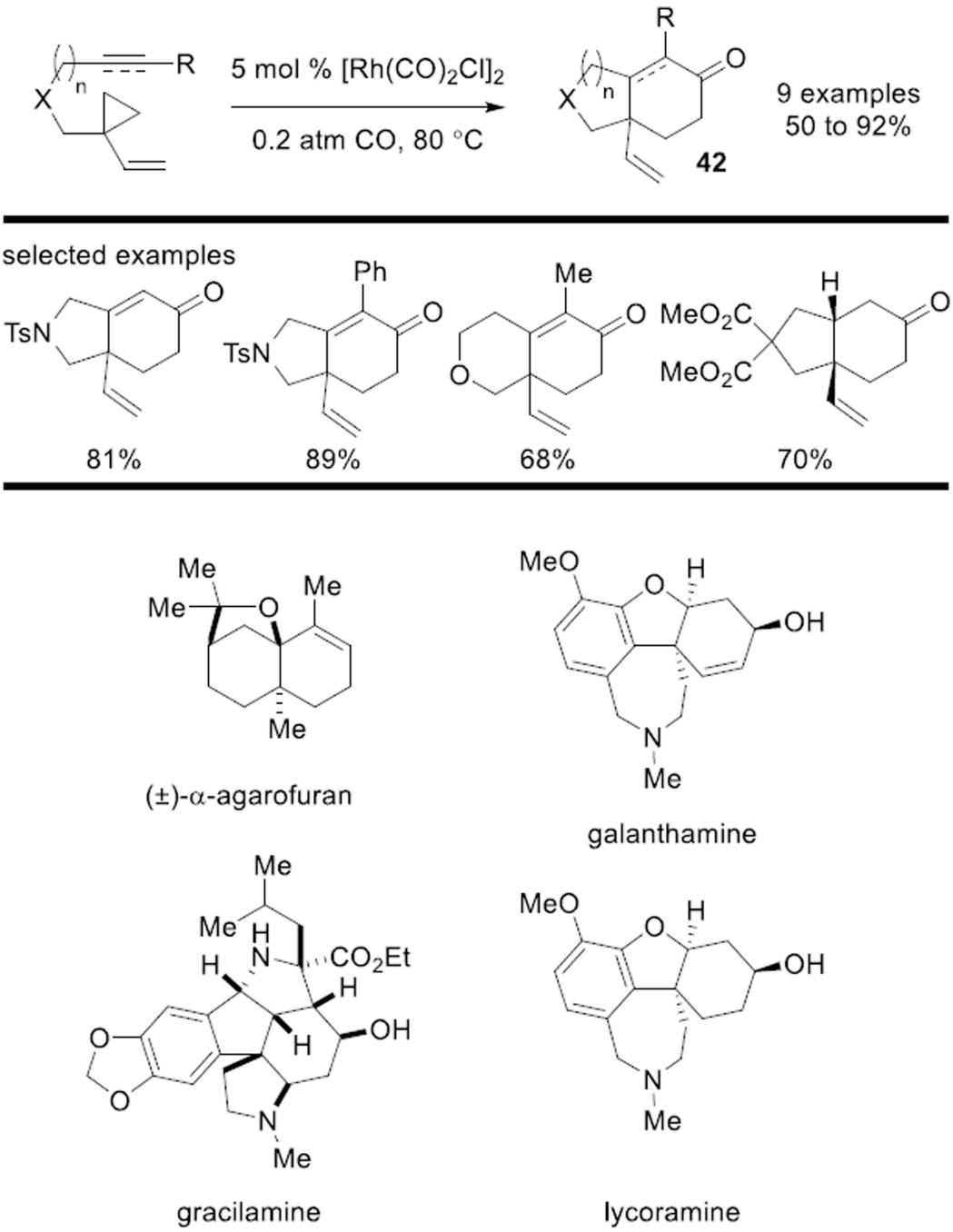

**Scheme 23.**
Rh-catalyzed [3+2] cycloaddition of 1-substituted-VCPs.



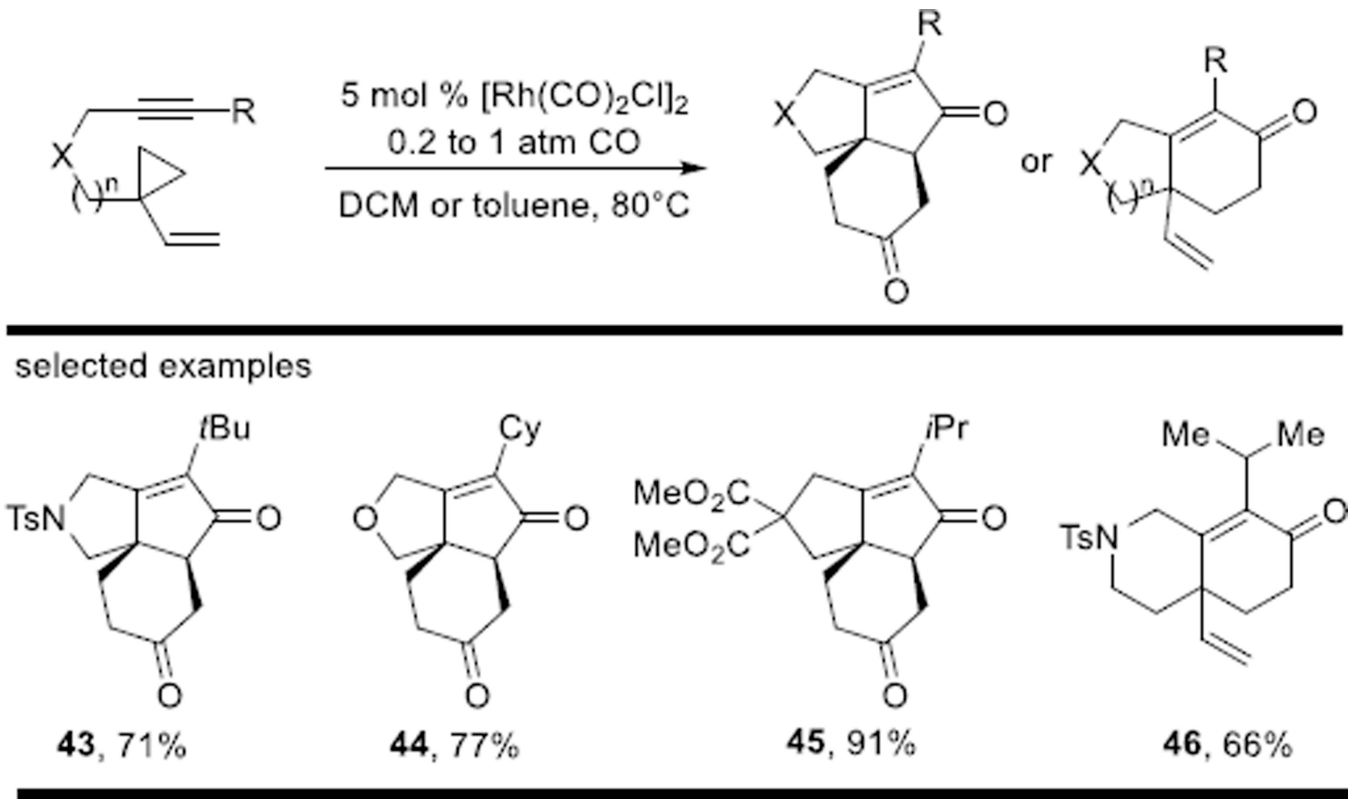

**Scheme 24.**
Reaction mechanism of the [3+2] cycloaddition of 1-substituted-VCPs




**Scheme 25.**
Asymmetric [3+2] cycloaddition of 1-substituted-VCPs

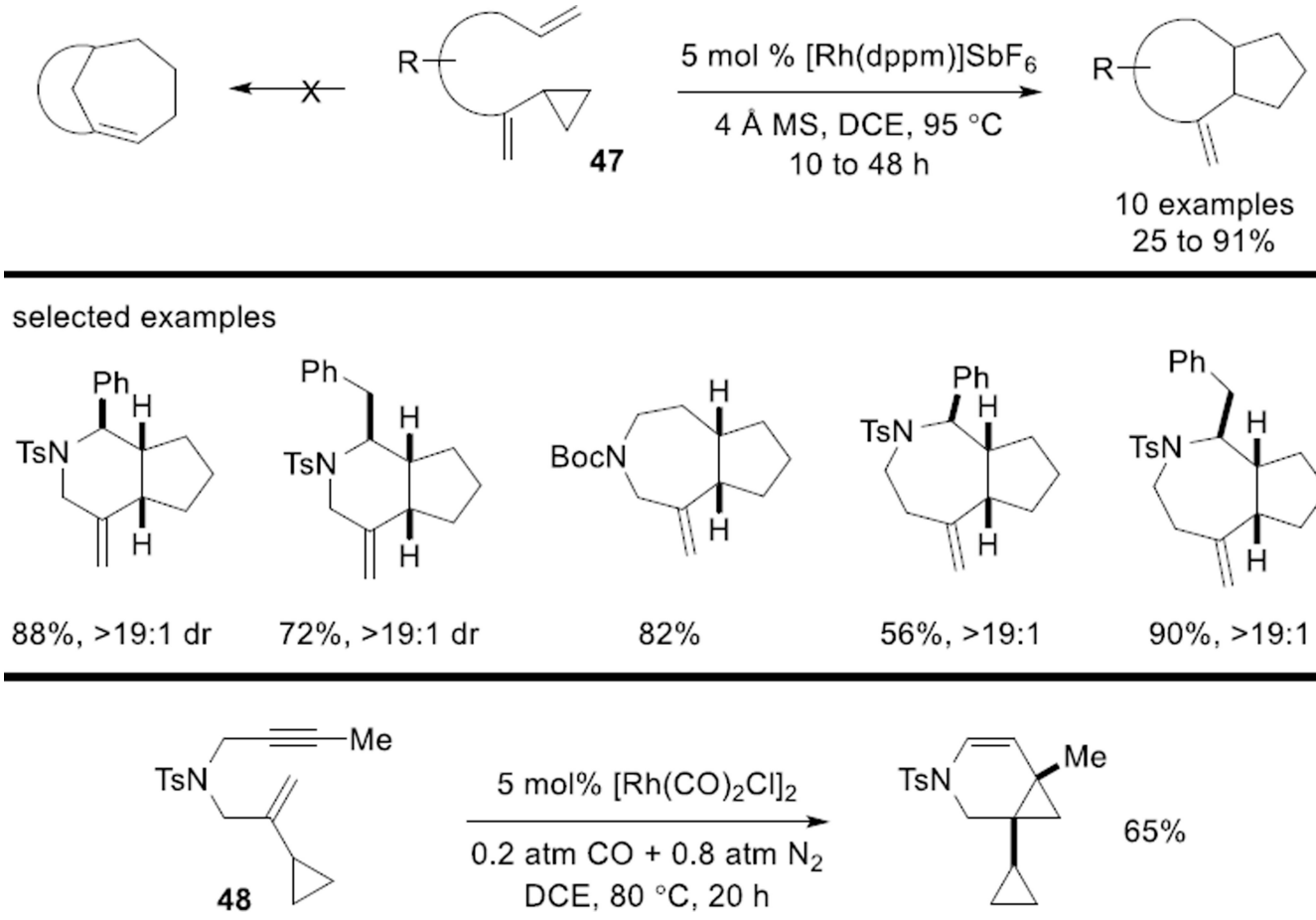



**Scheme 26.**
Carbonylative [3+2+1] cycloadditions of 1-substituted-VCPs.

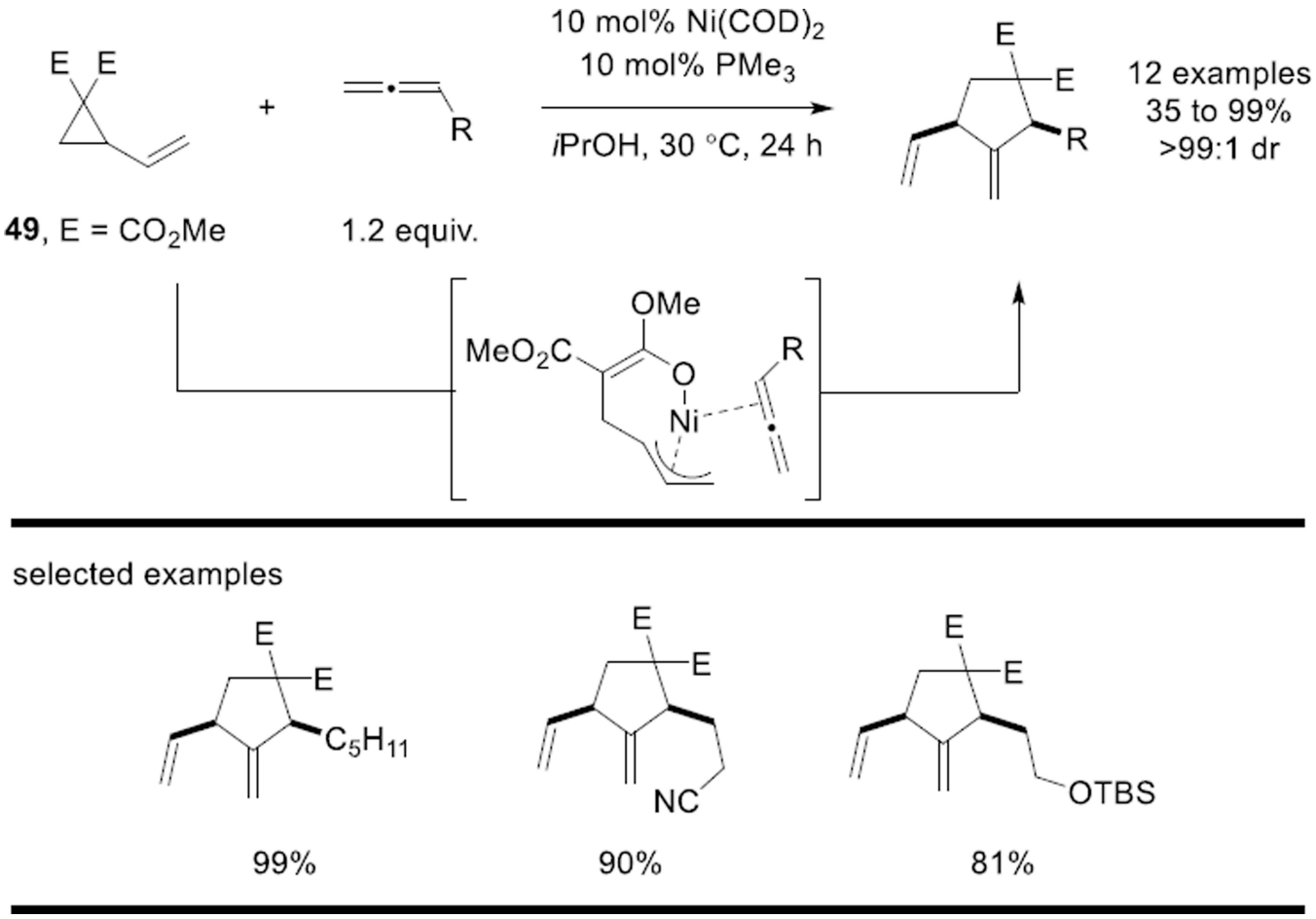



**Scheme 27.**

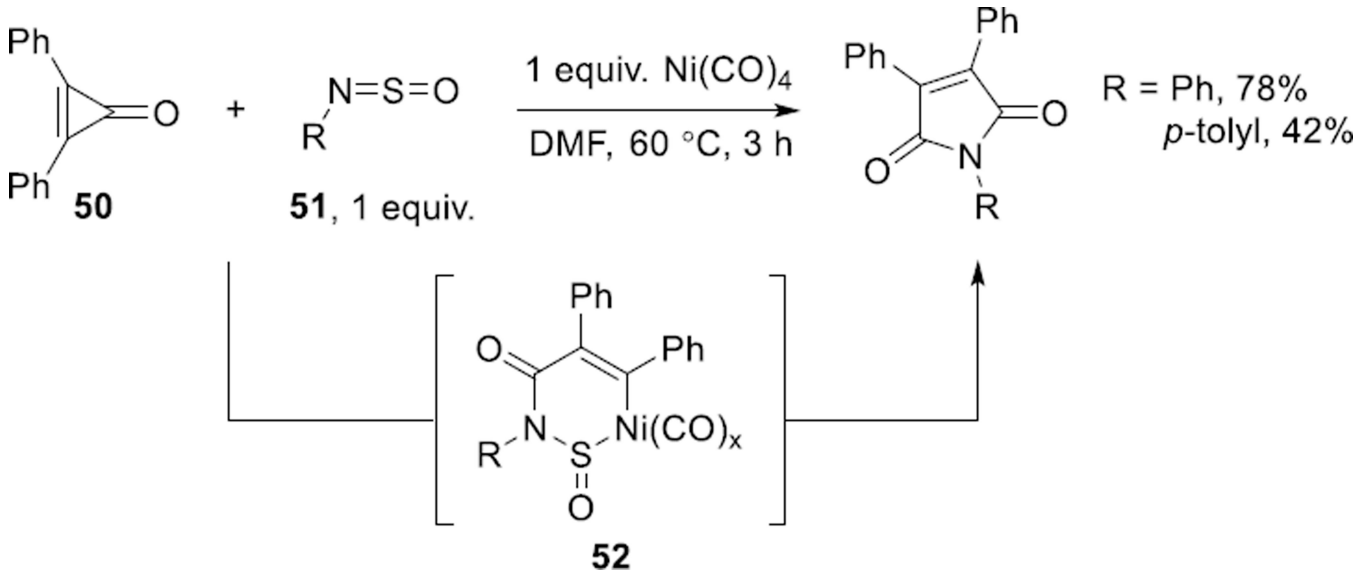
Carbonylative [5 + 1]/[2 + 2 + 1] or [3+2+1] cycloadditions of 1-substituted-VCPs



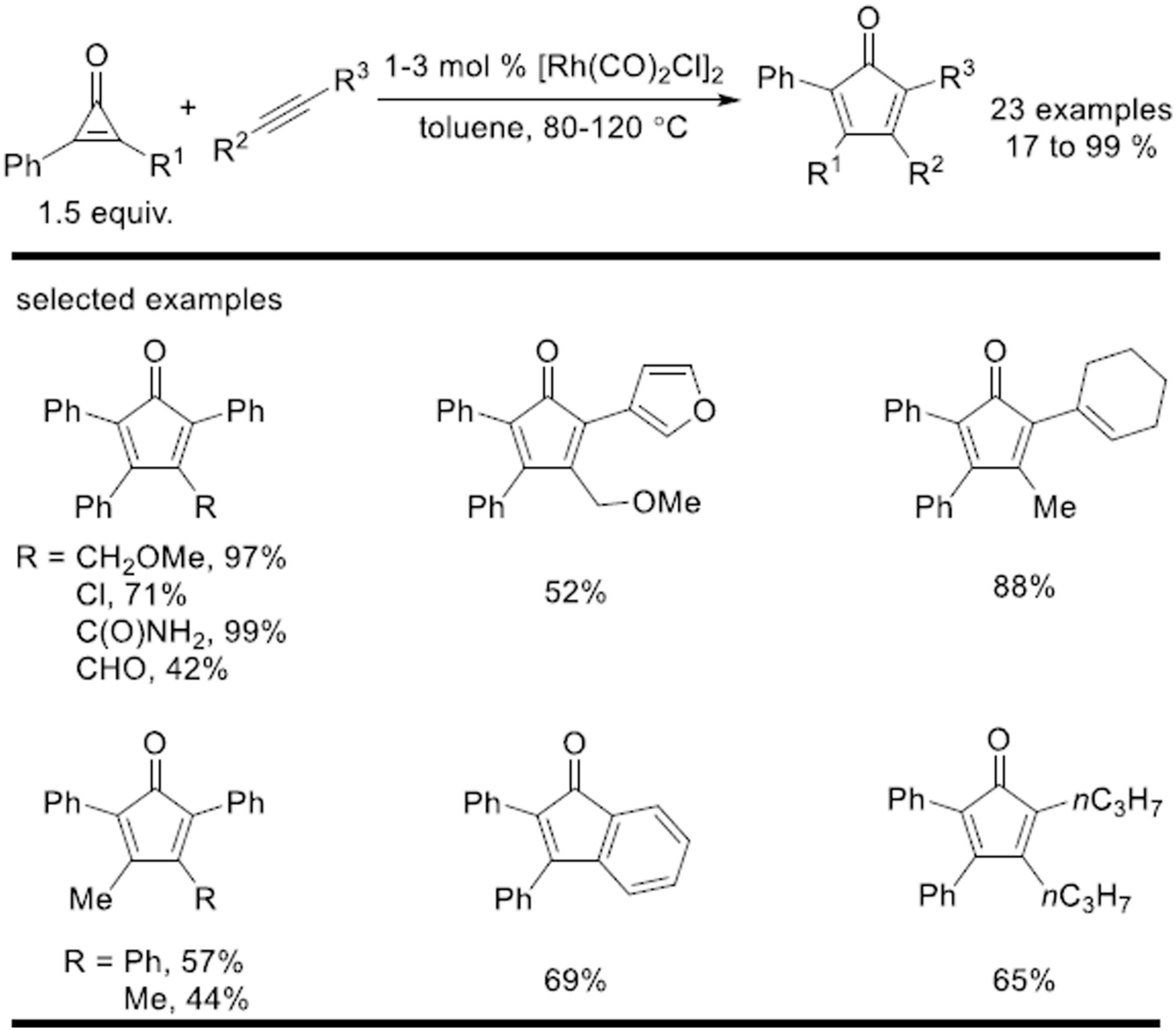

**Scheme 28.**
[3+2] cycloaddition of α-substituted-VCPs



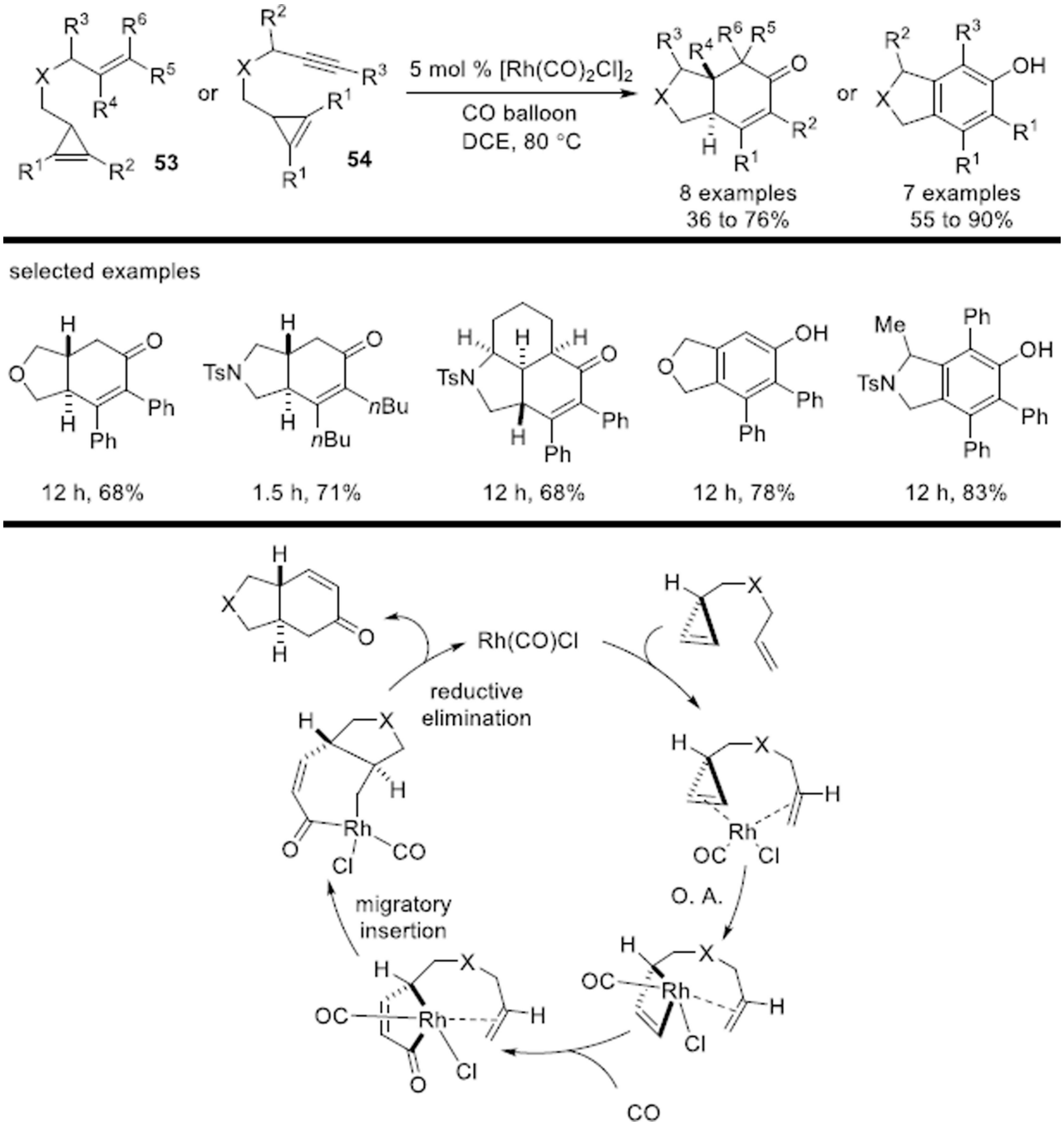

**Scheme 29.**
Ni-catalyzed intermolecular [3+2] cycloaddition between VCPs and allenes



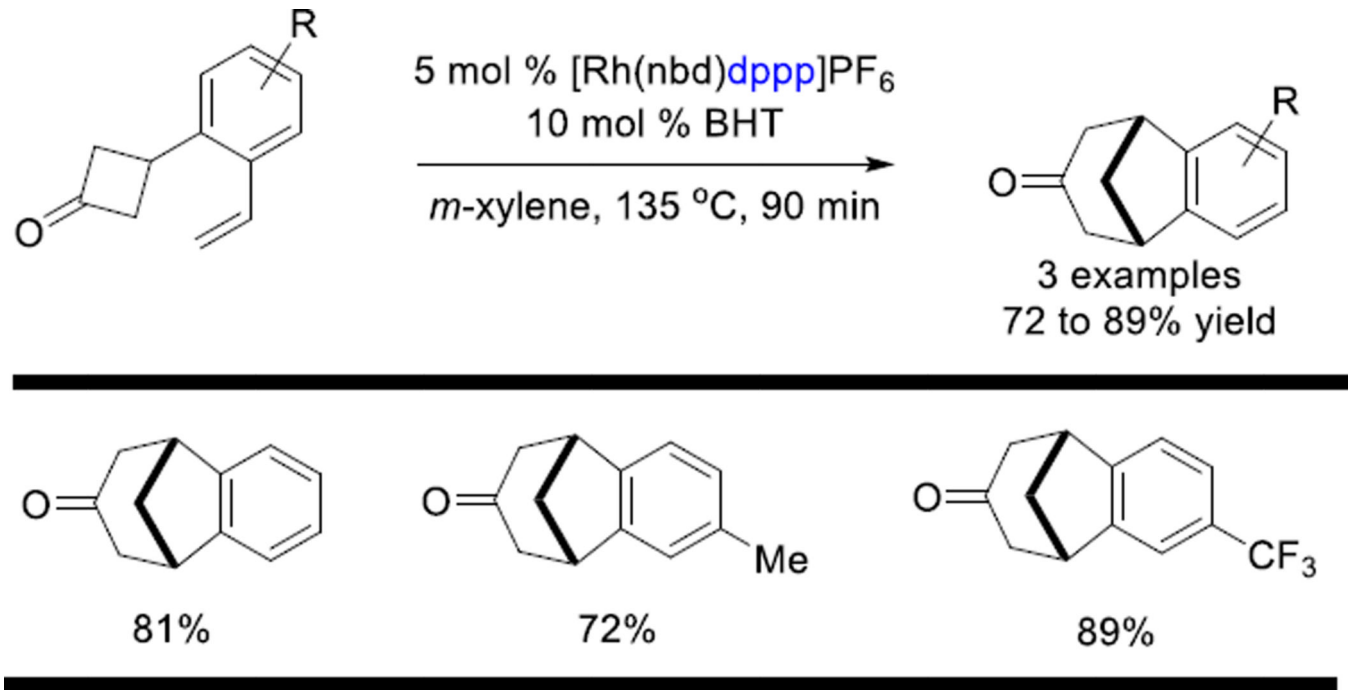

**Scheme 30.**
Cyclopropenone-mediated cycloaddition



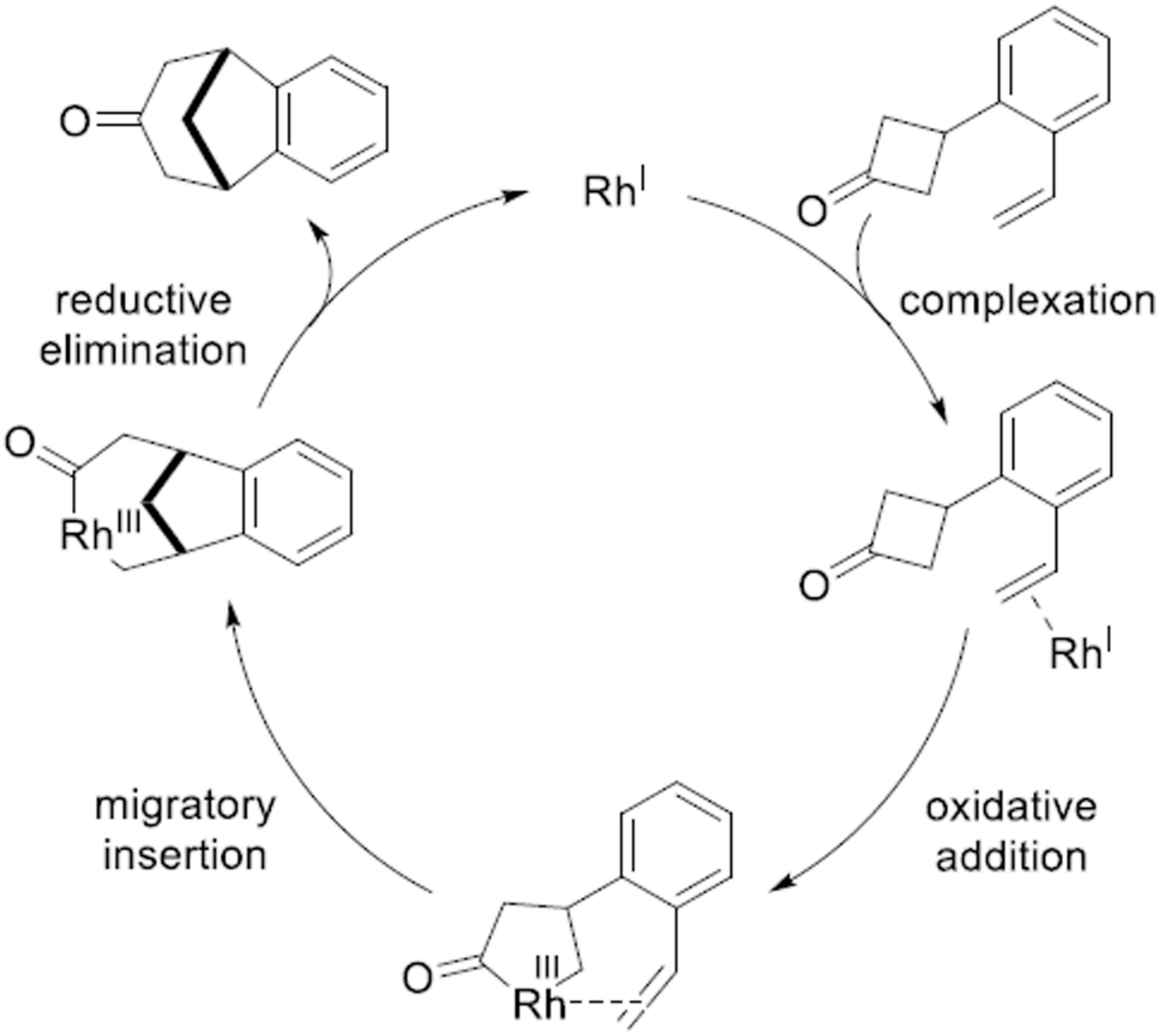

**Scheme 31.**
Intermolecular [3+2] cycloaddition between cyclopropenones and alkynes



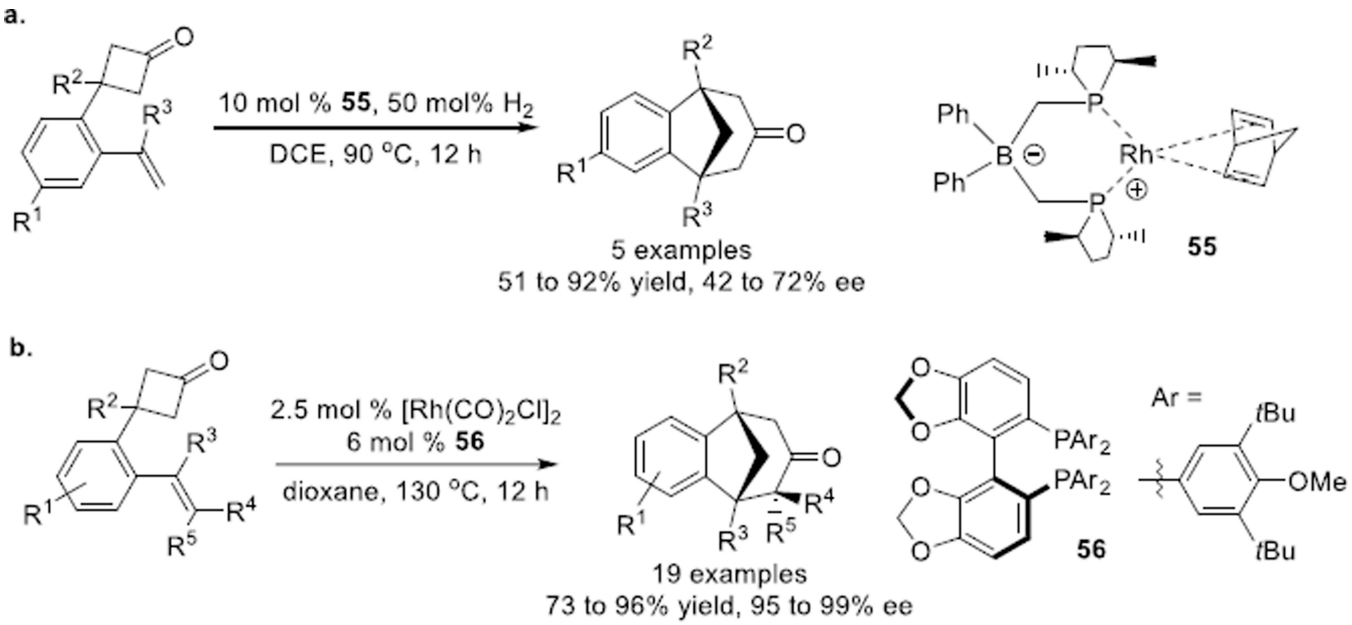

**Scheme 32.**
Intramolecular [3+2] cycloaddition of cyclopropenes




**Scheme 33.**
Carboacylation with the styrene-tethered cyclobutanones

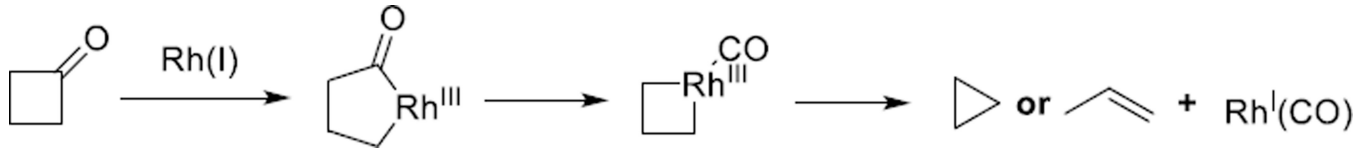



**Scheme 34.**
Proposed pathway for the Rh-catalyzed carboacylation of the styrene-tethered cyclobutanones

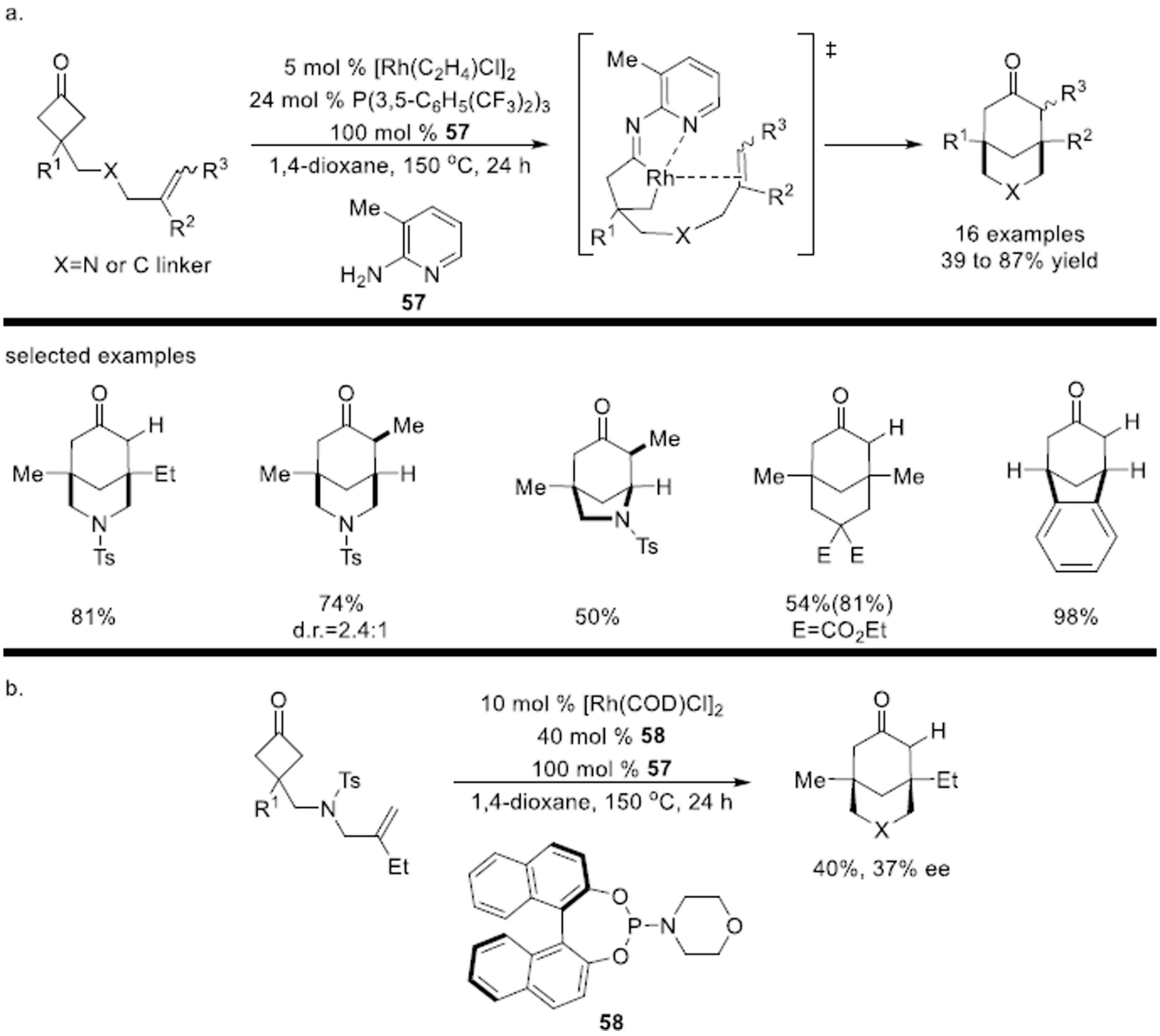



**Scheme 35.**

Enantioselective carboacylation of the styrene-tethered cyclobutanones

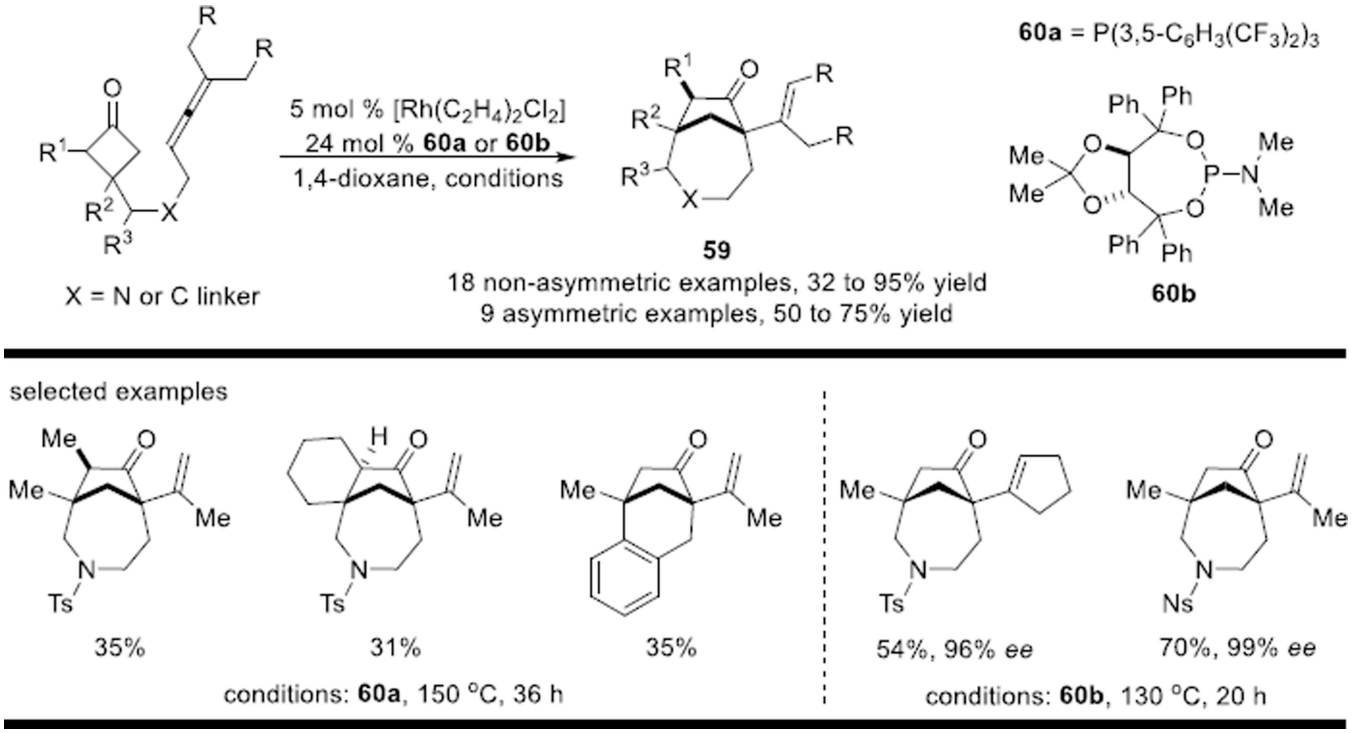



**Scheme 36.**
Competing decarbonylation pathway

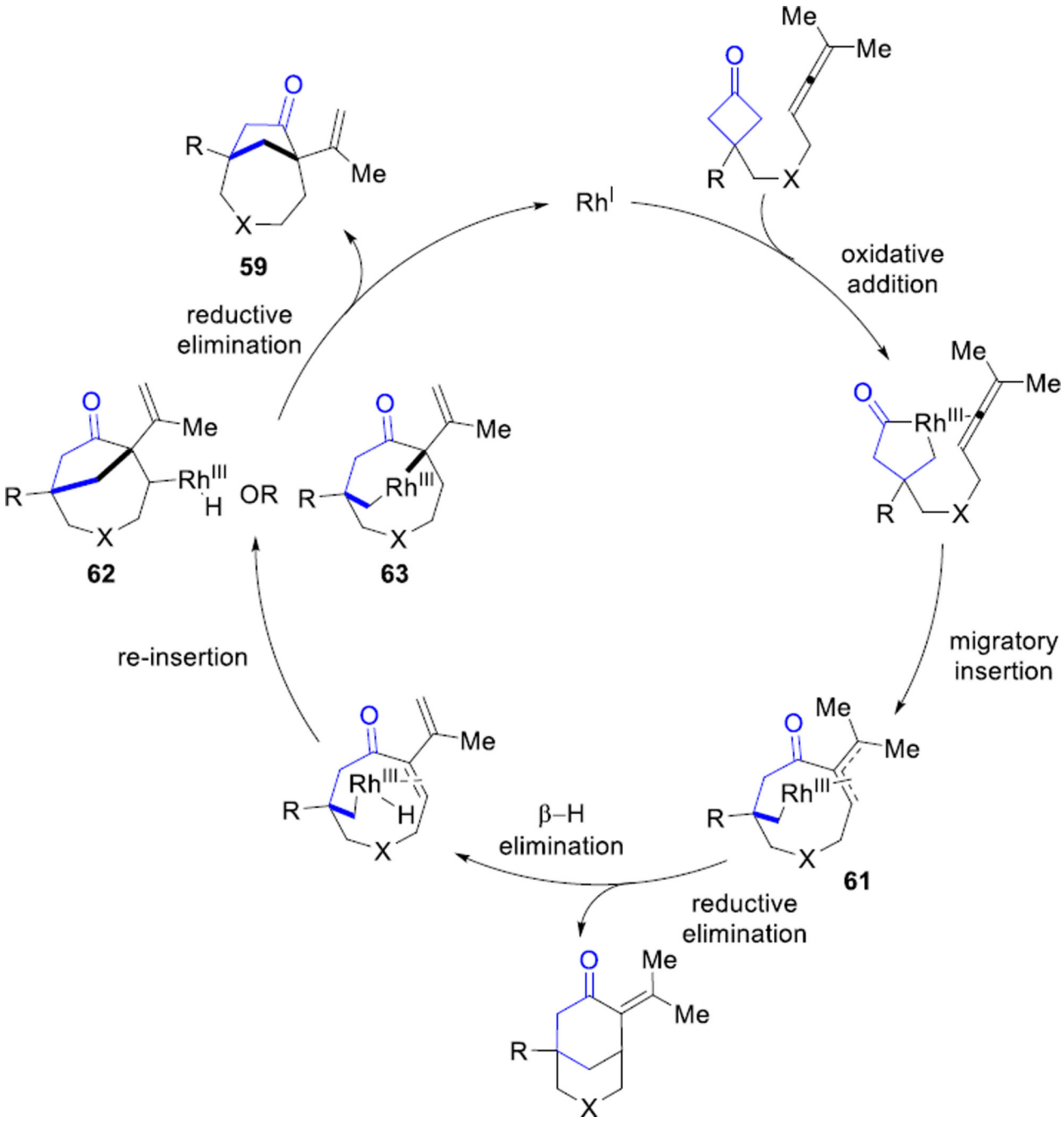



**Scheme 37.**

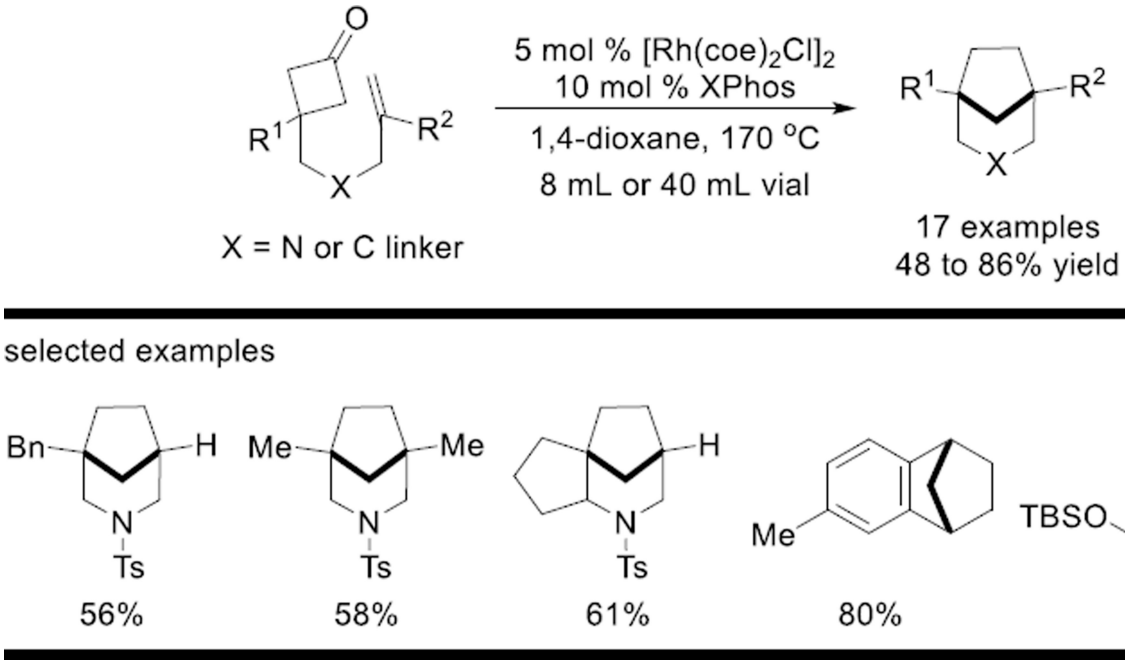
A temporary DG-based strategy for the “cut and sew” reaction with cyclobutanones and olefins



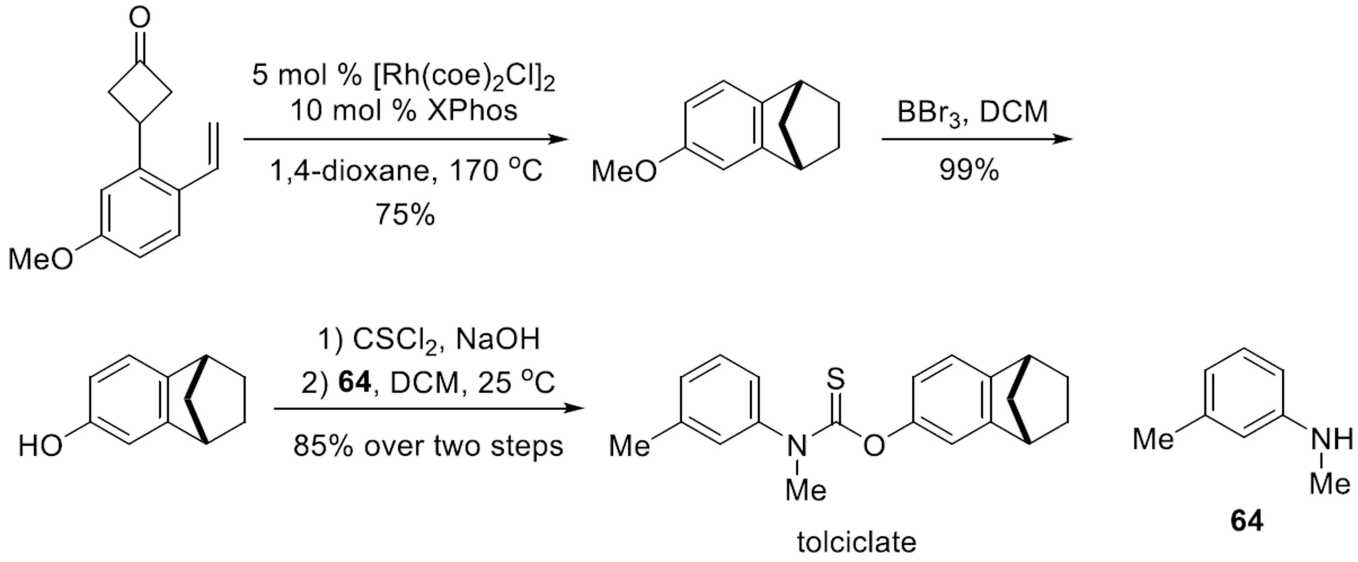

**Scheme 38.**
[4+1] cycloaddition of cyclobutanones and allenes



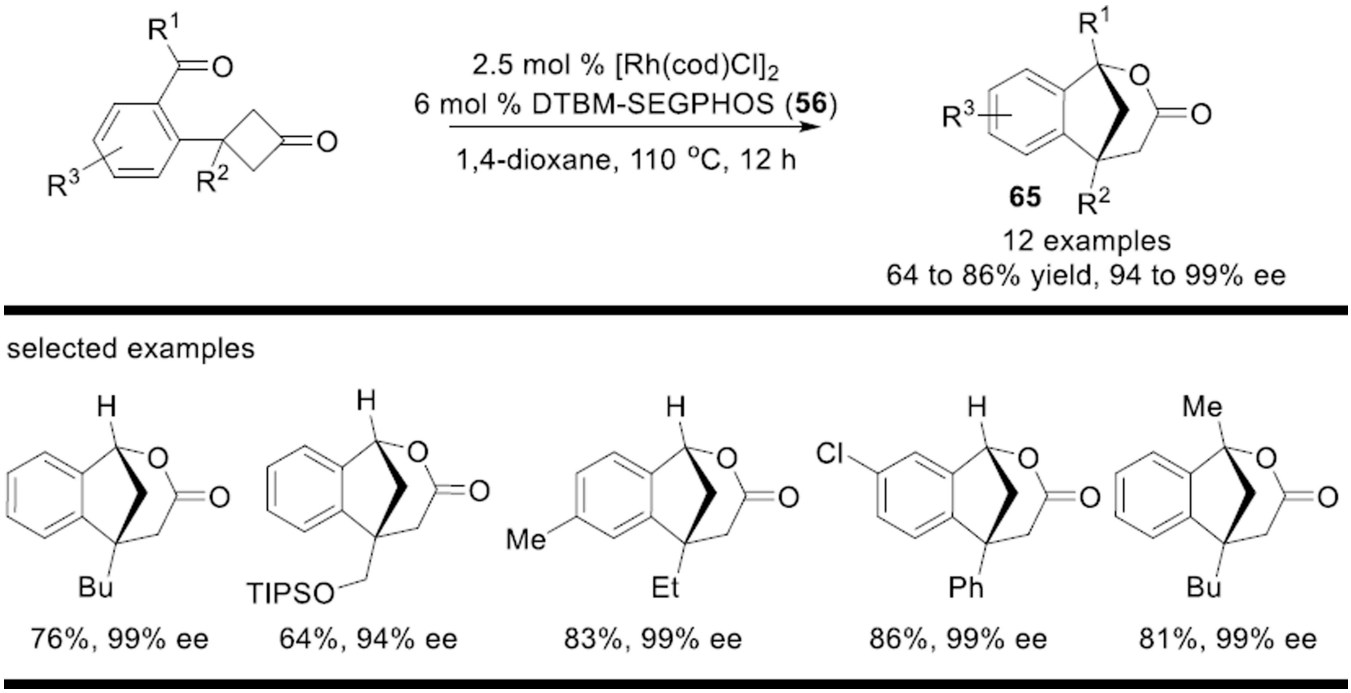

**Scheme 39.**
Proposed mechanism of the [4+1] cycloaddition of cyclobutanones and allenes



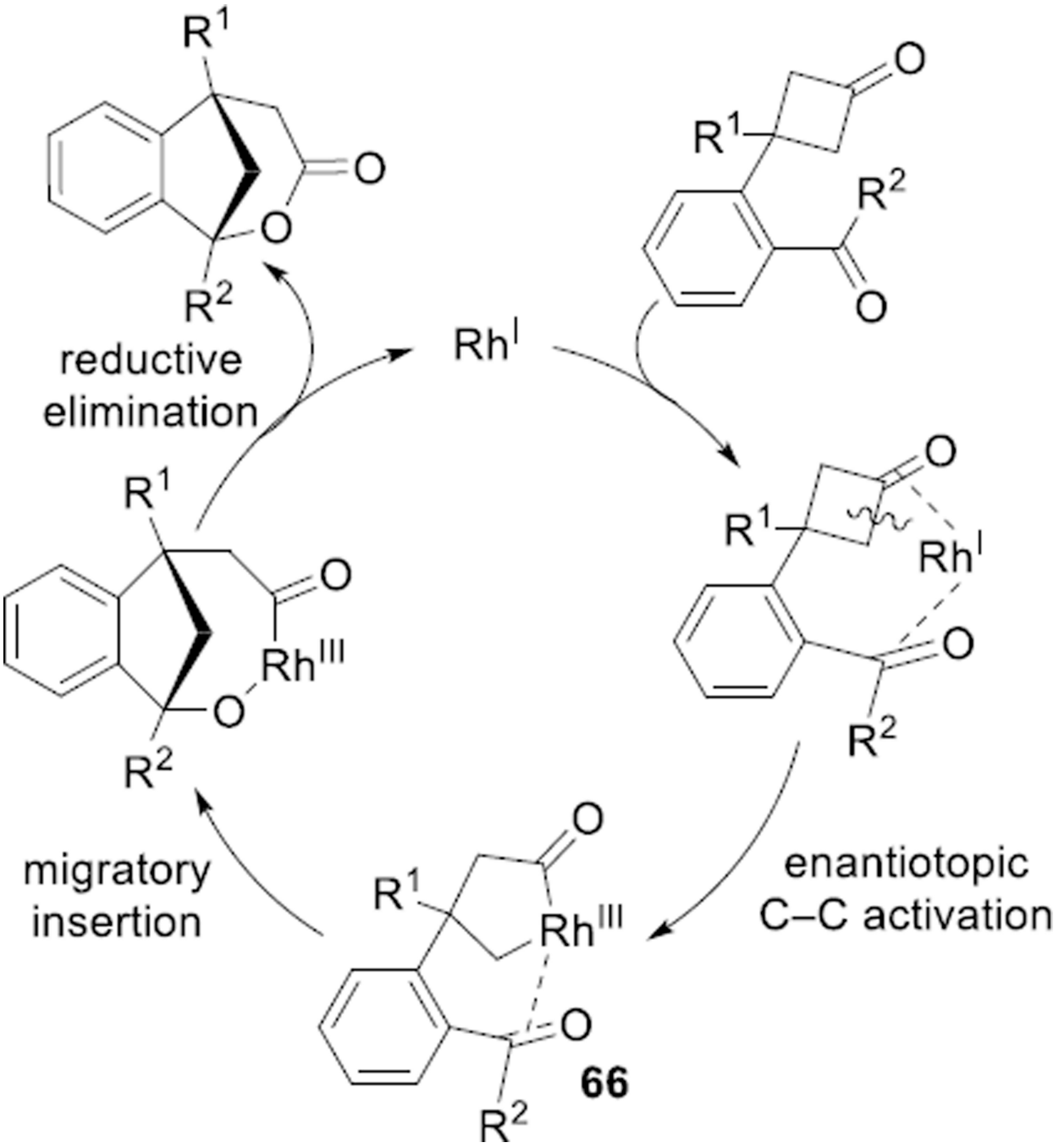

**Scheme 40.**
Rhodium-catalyzed [4+2-1] cycloaddition



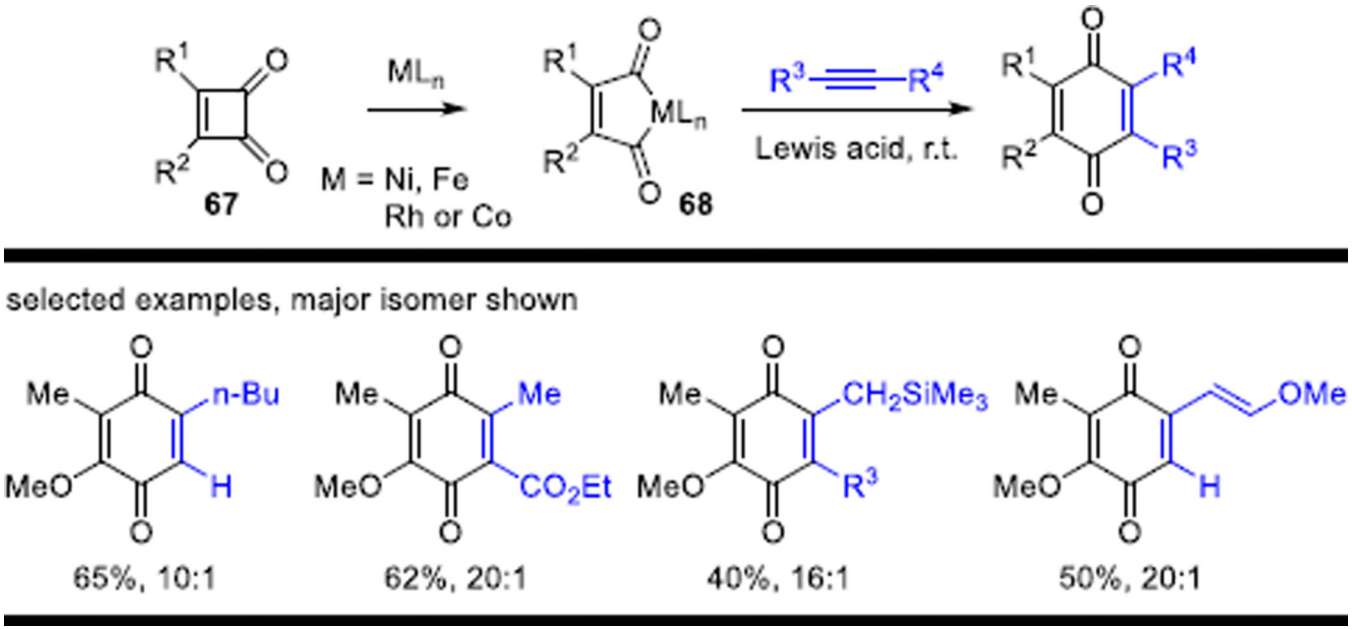

**Scheme 41.**
Synthesis of tolciclate



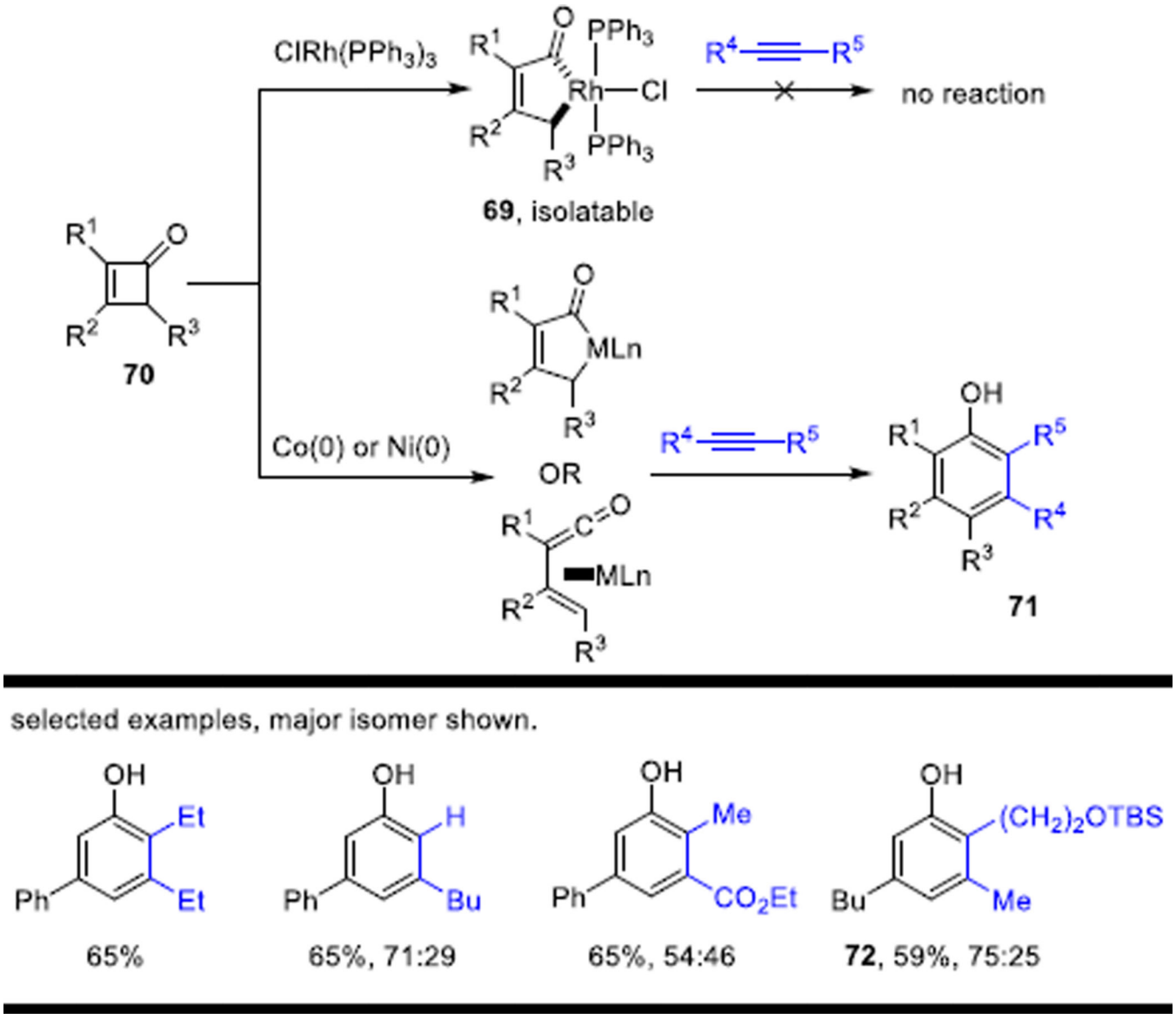

**Scheme 42.**
Asymmetric carbonyl insertion to cyclobutanone



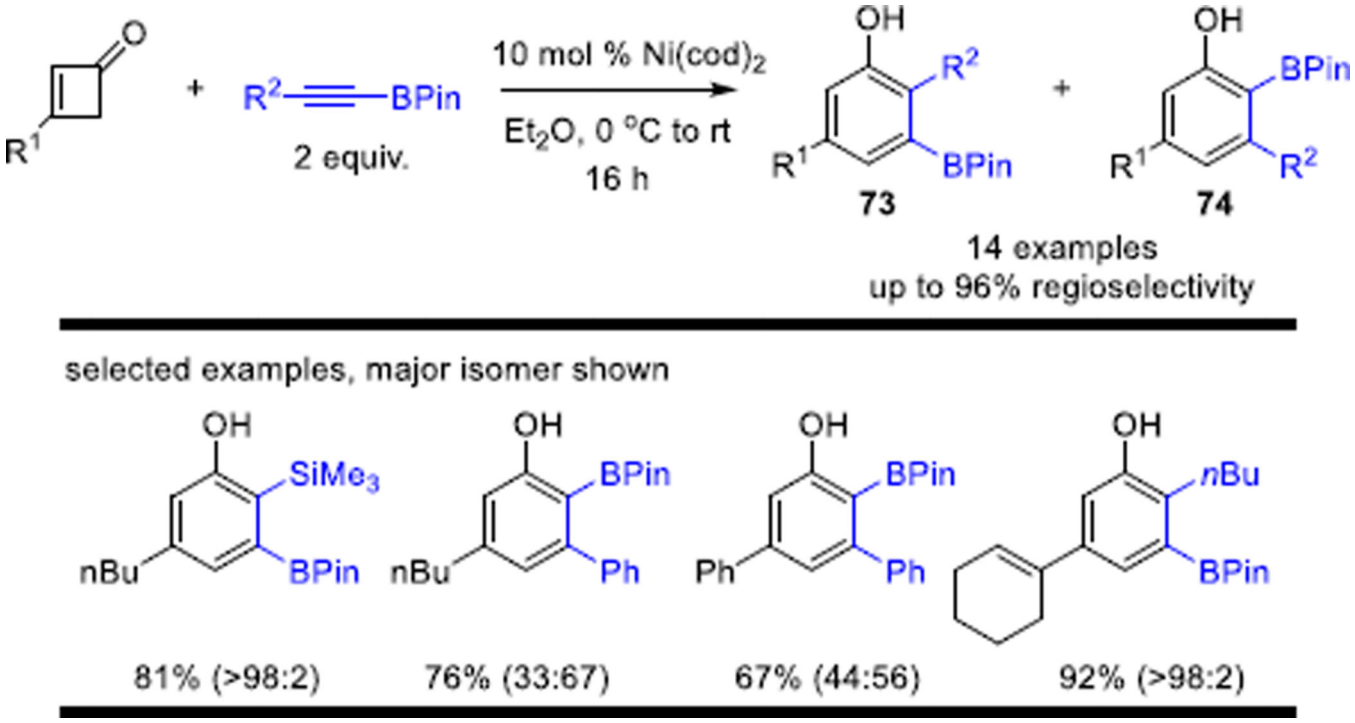

**Scheme 43.**
Proposed catalytic cycle of the Rh-catalyzed carbonyl-cyclobutanone coupling



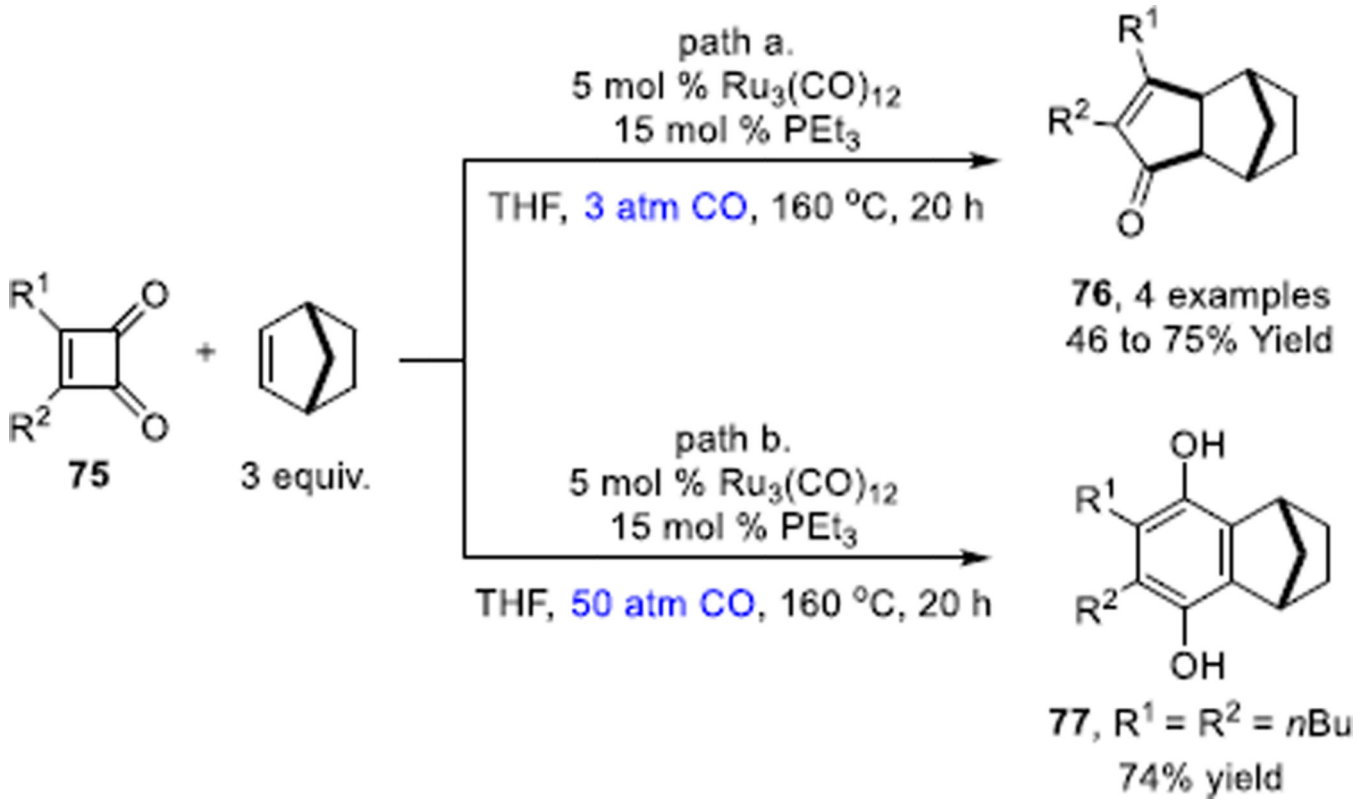

**Scheme 44.**
Quinone synthesis from C–C activation of cyclobutenediones



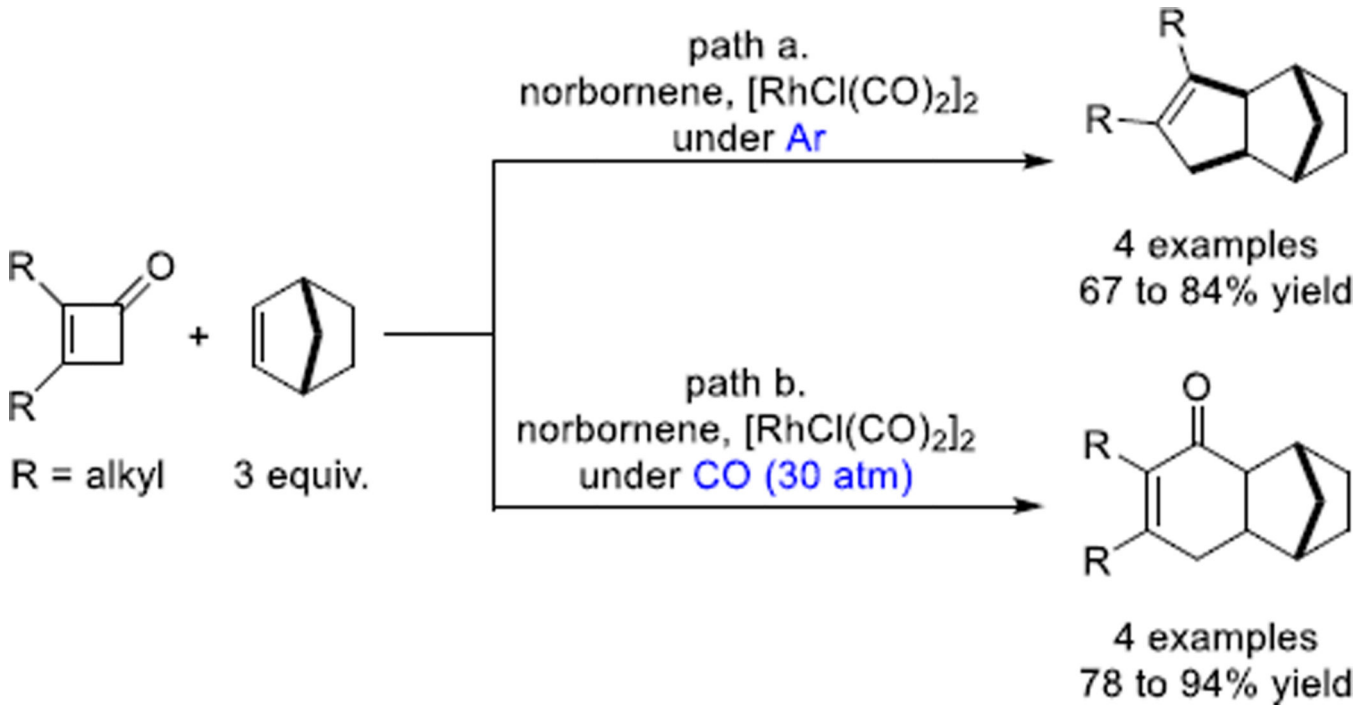

**Scheme 45.**
Phenol synthesis from C–C activation of cyclobutenones



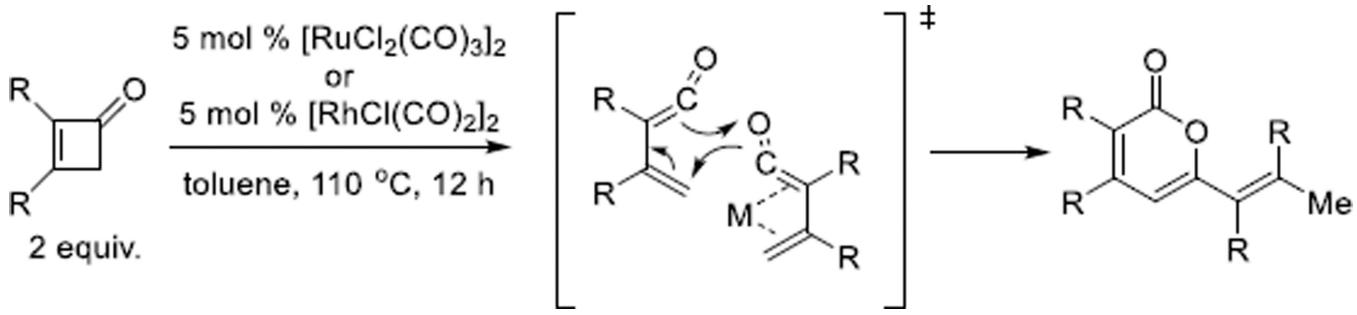

**Scheme 46.**
Alkynyl boronate insertion into cyclobutenones



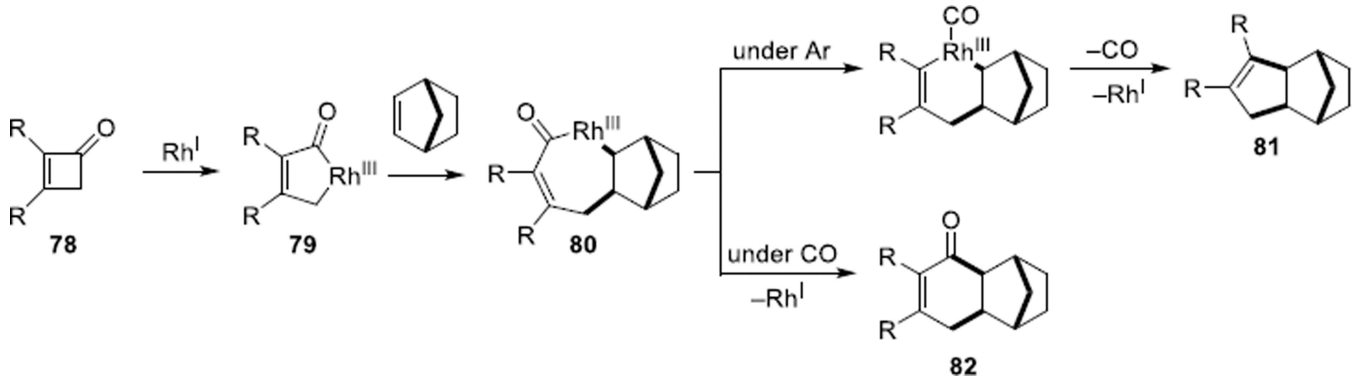

**Scheme 47.**
Norbornene insertion into cyclobutenediones



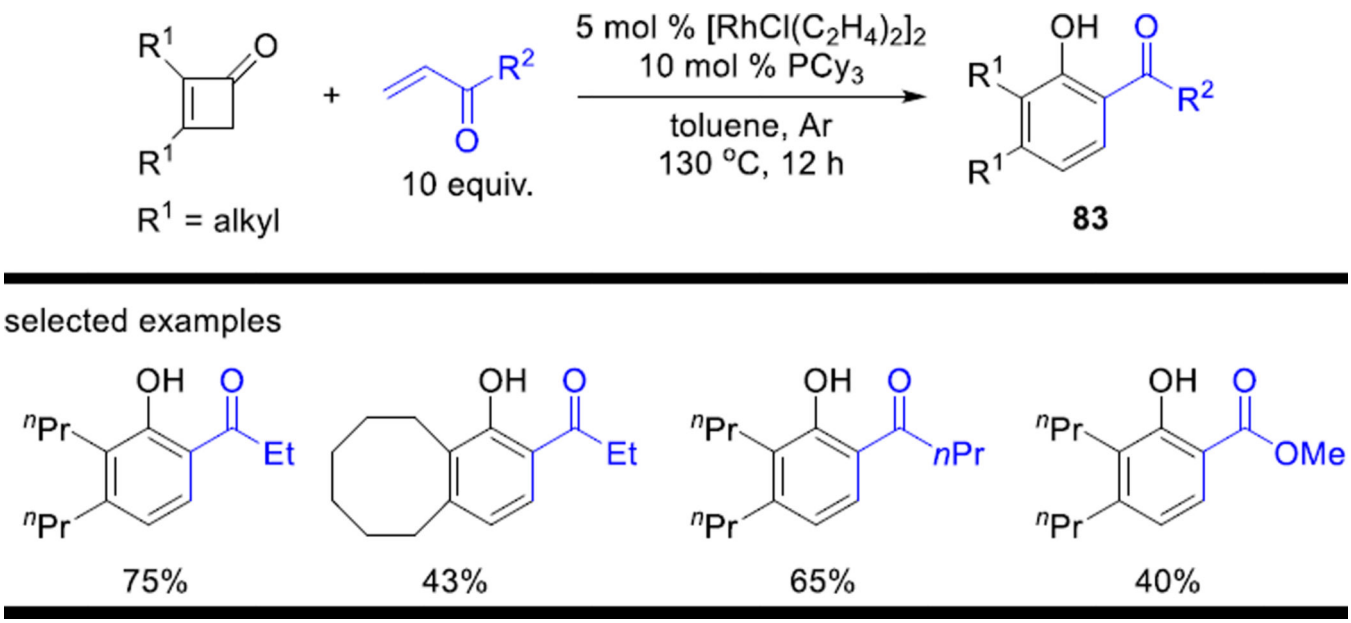

**Scheme 48.**
Rh-catalyzed norbornene-cyclobutenone coupling



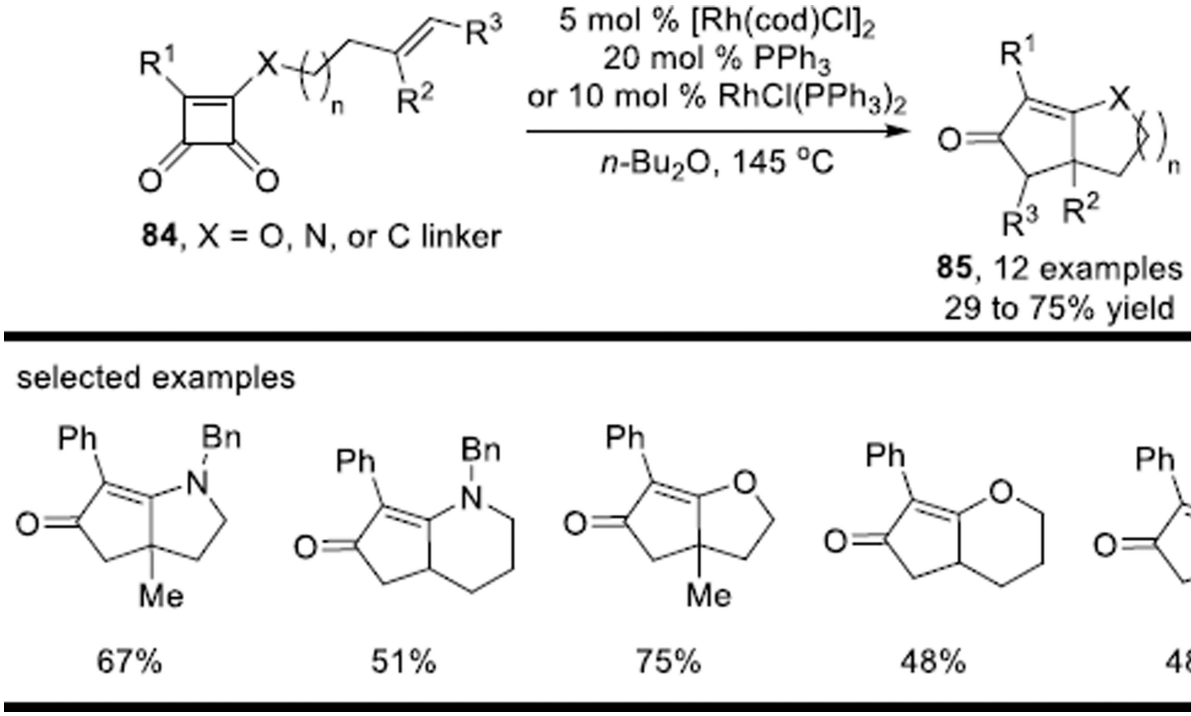

**Scheme 49.**
Cyclobutenone dimerization



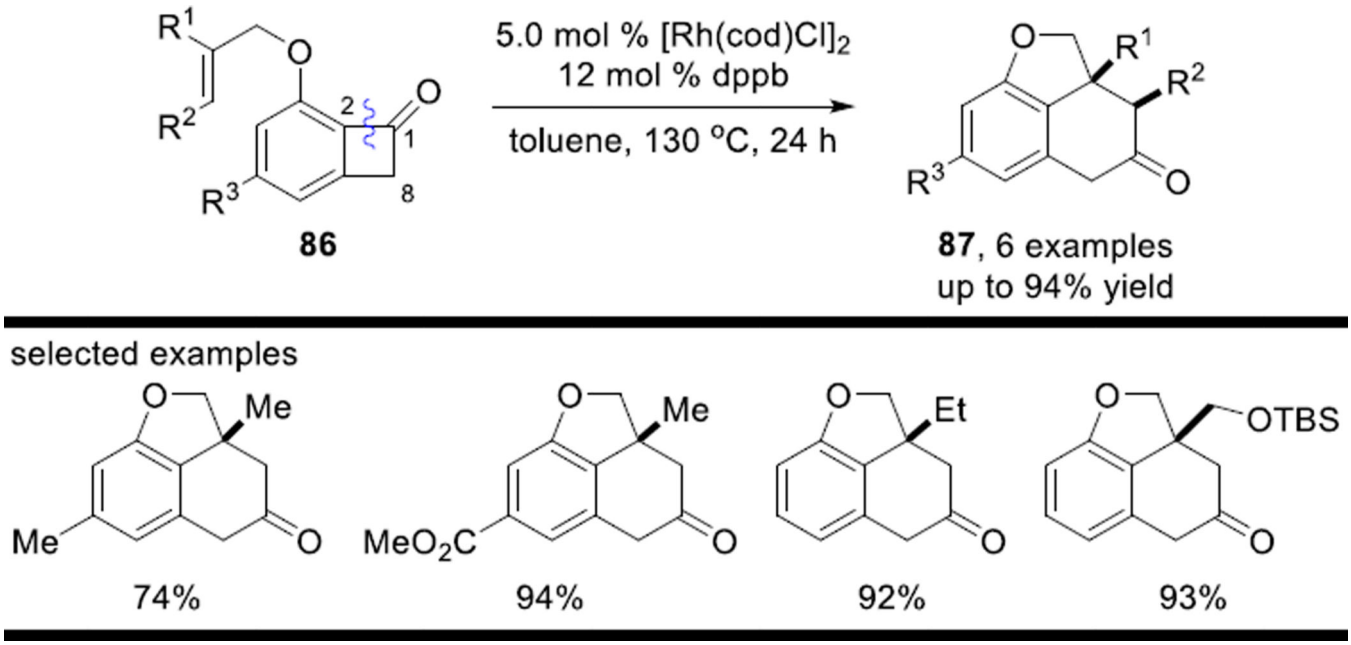

**Scheme 50.**
Proposed reaction pathway of the norbornene-cyclobutenone coupling




**Scheme 51.**
Coupling of electron-deficient olefins with cyclobutenones

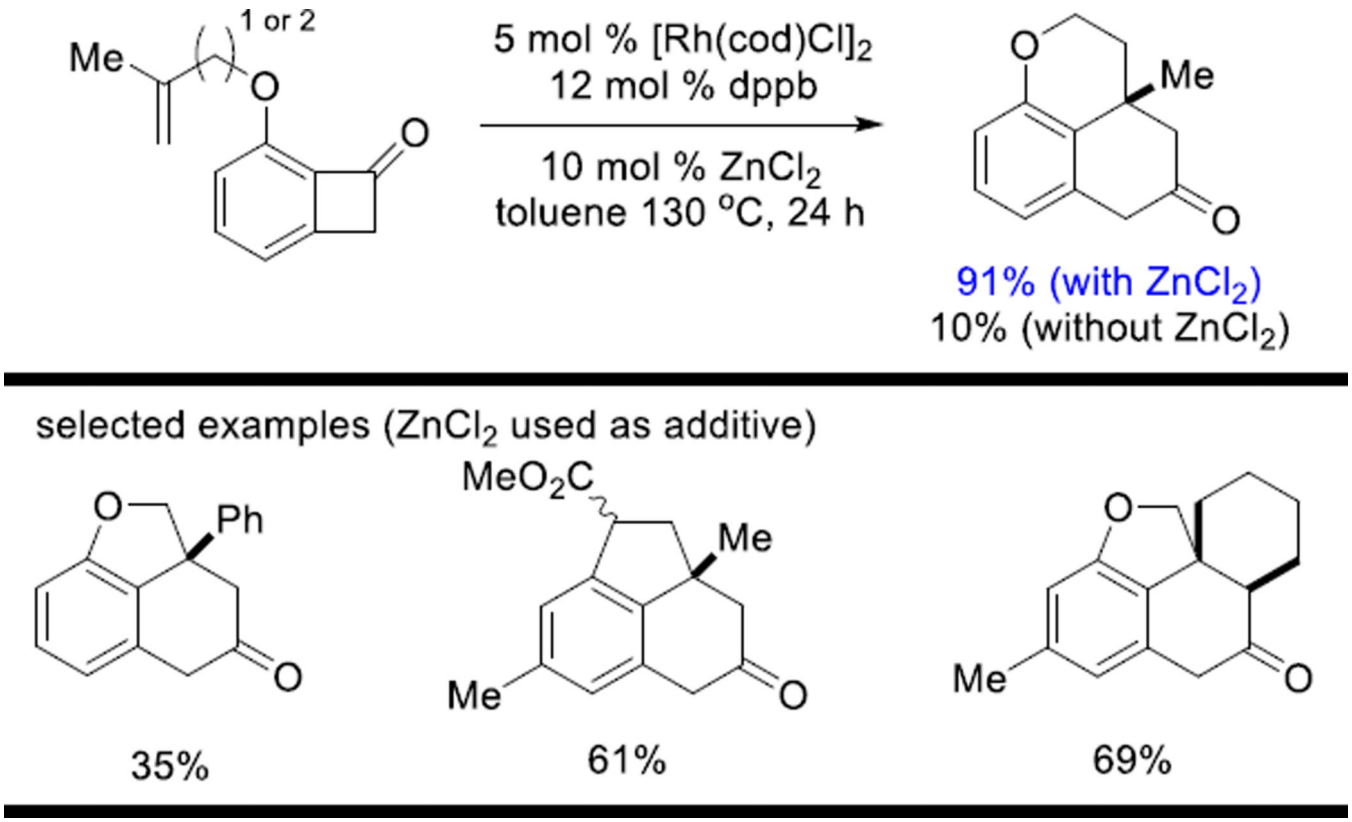



**Scheme 52.**
Intramolecular decarbonylative alkene insertion with cyclobutenediones

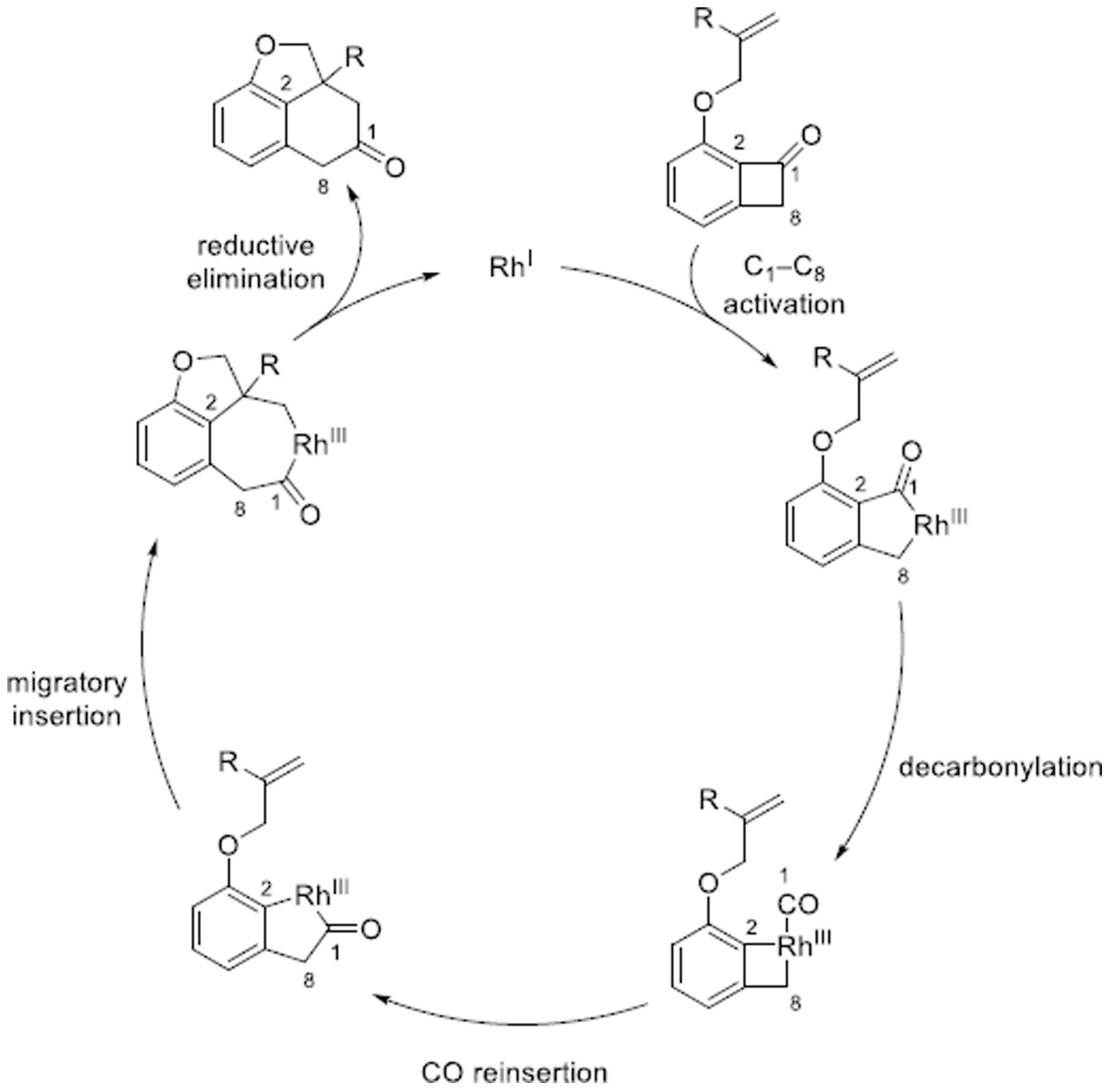



**Scheme 53.**

Selective proximal $C_1$–$C_2$ cleavage of benzocyclobutenones and tethered olefin insertion

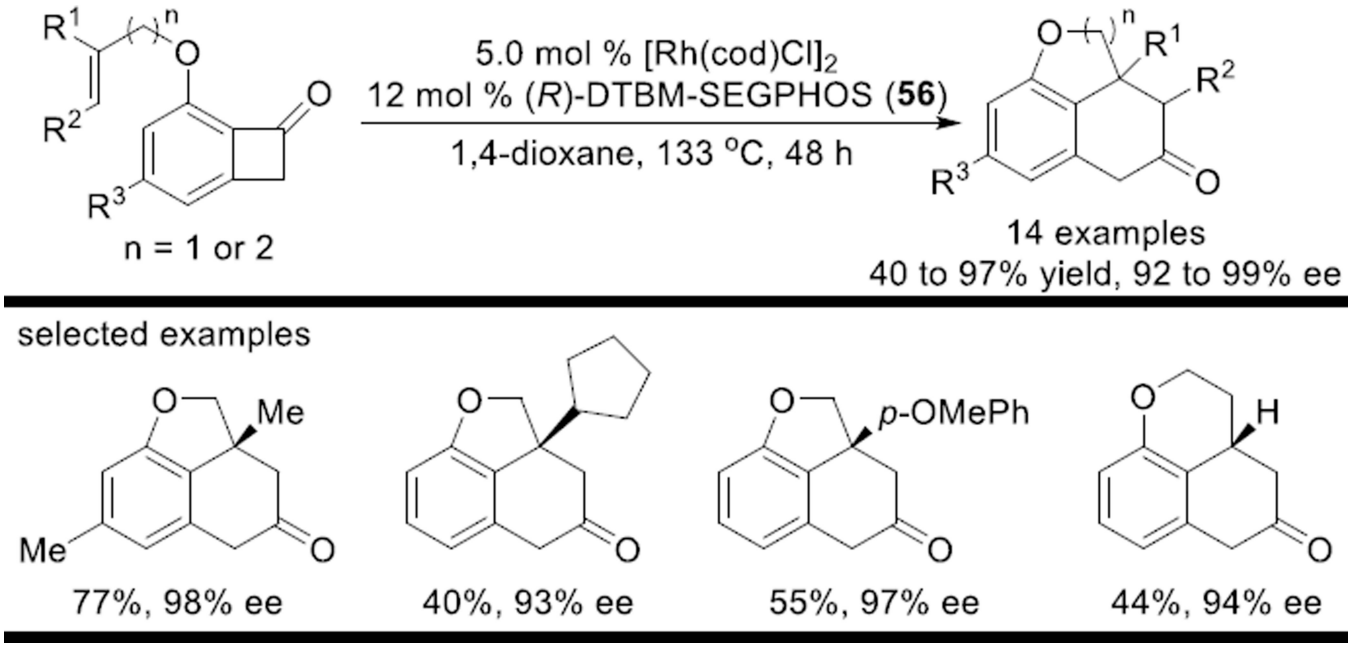



**Scheme 54.**
Effect of $ZnCl_2$ on challenging olefin substrates

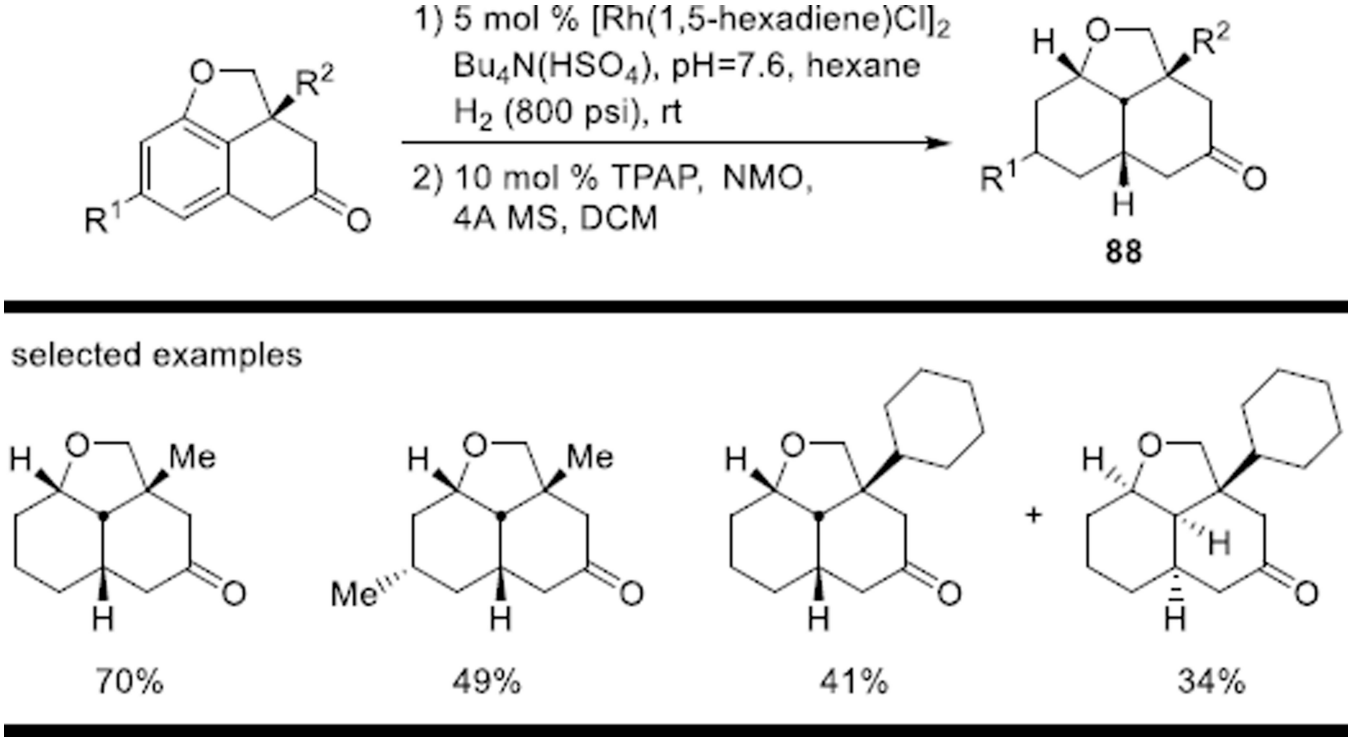



**Scheme 55.**

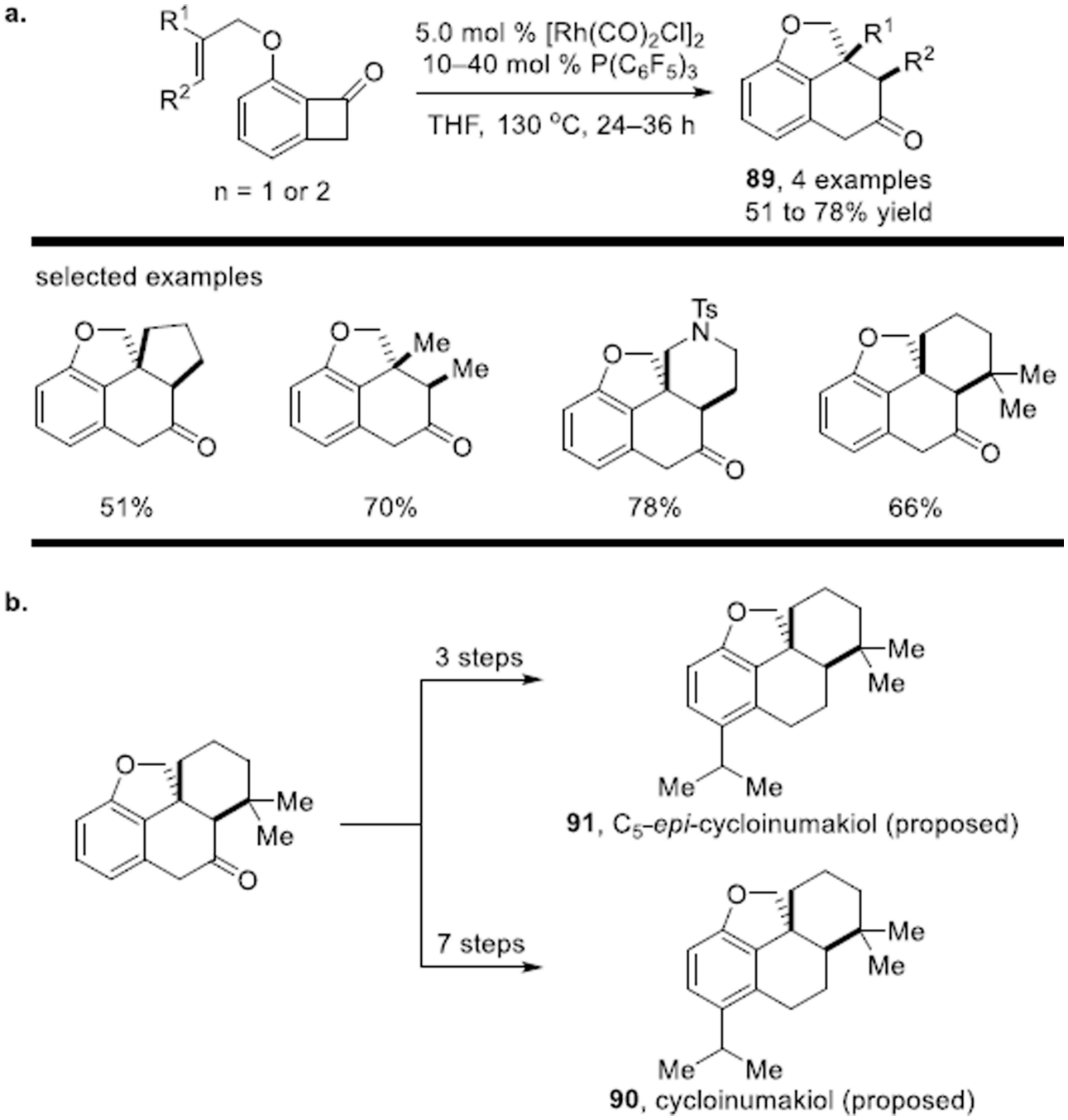
Indirect proximal $C_1$–$C_2$ activation through decarbonylative CO migration




**Scheme 56.**
Enantioselective “cut and sew” transformation with benzocyclobutenones

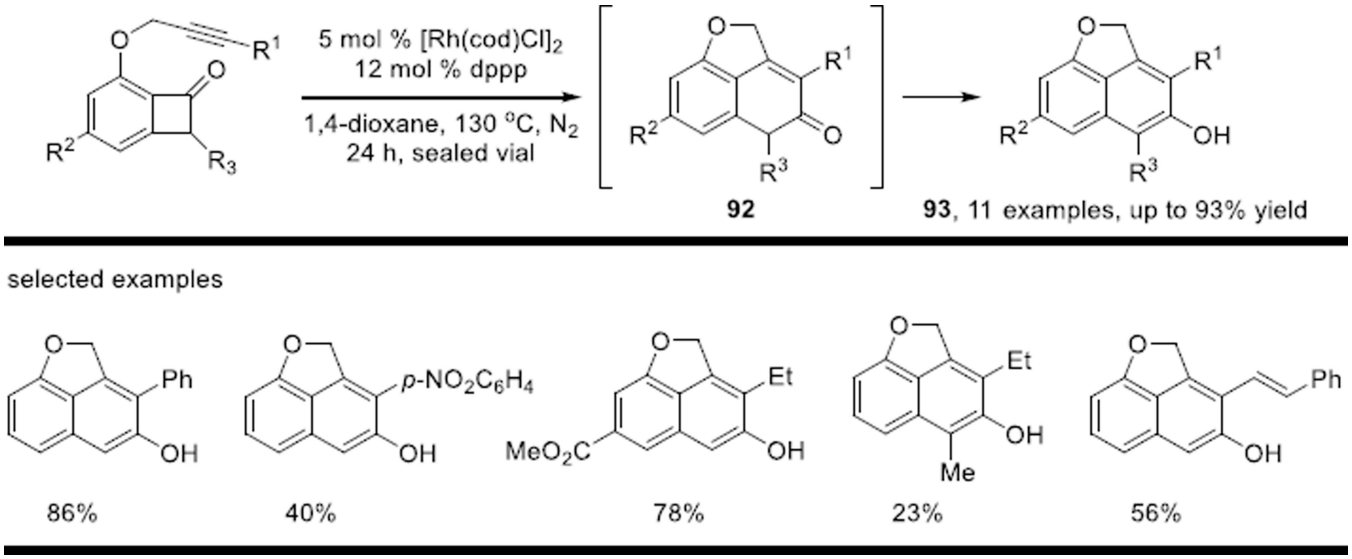



**Scheme 57.**
Reductive dearomatization of the tricyclic products

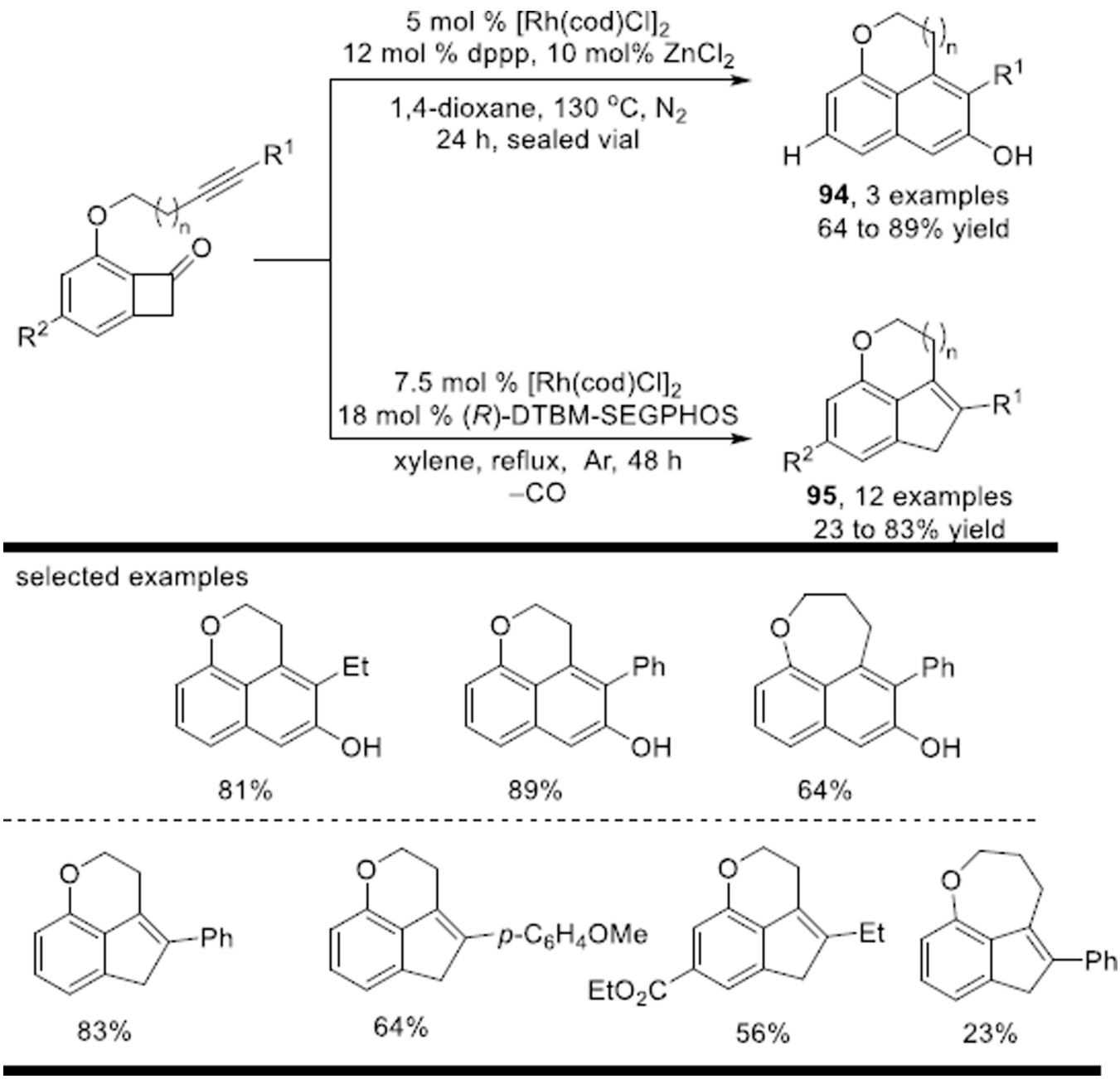



**Scheme 58.**

Coupling of trisubstituted olefins and its application in the total synthesis of cycloinumakiol

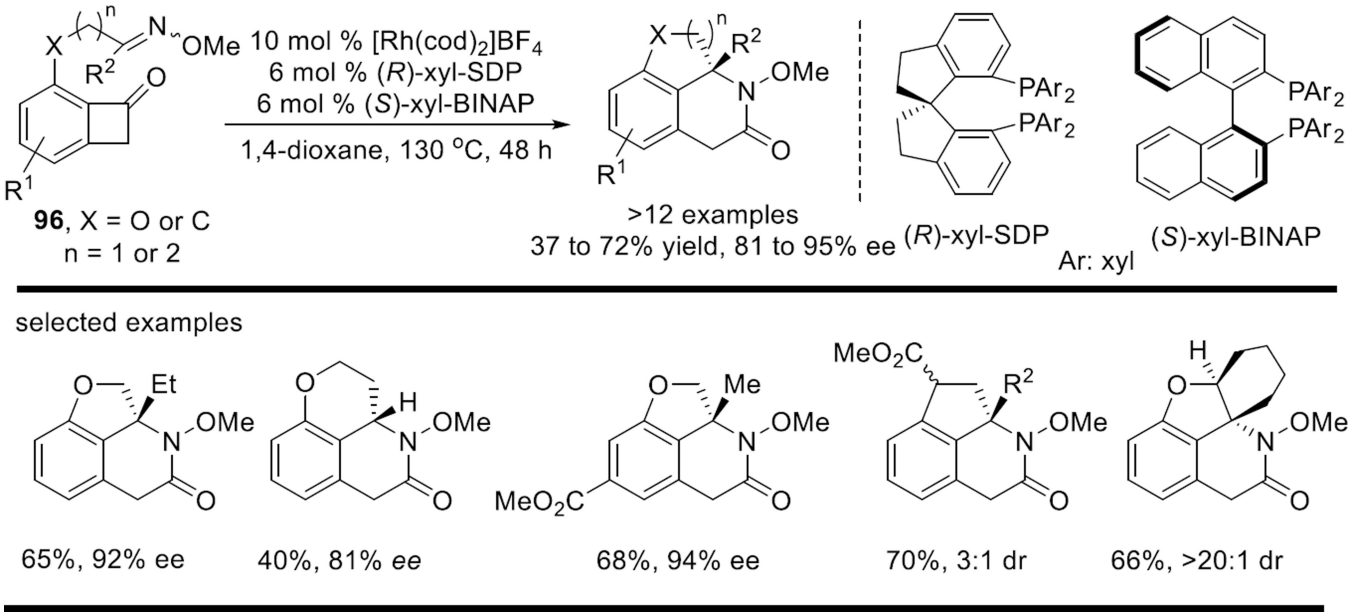



**Scheme 59.**
Alkyne insertion into benzocyclobutenones



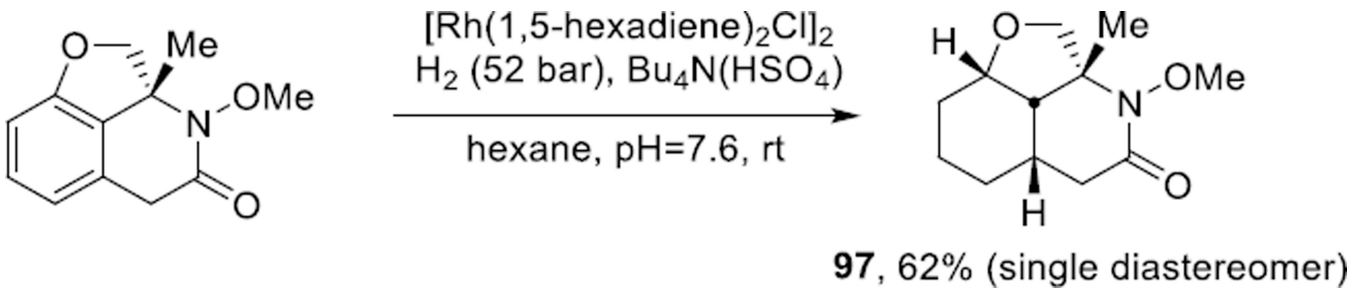

**Scheme 60.**

A divergent approach to access fused naphthols and indenes

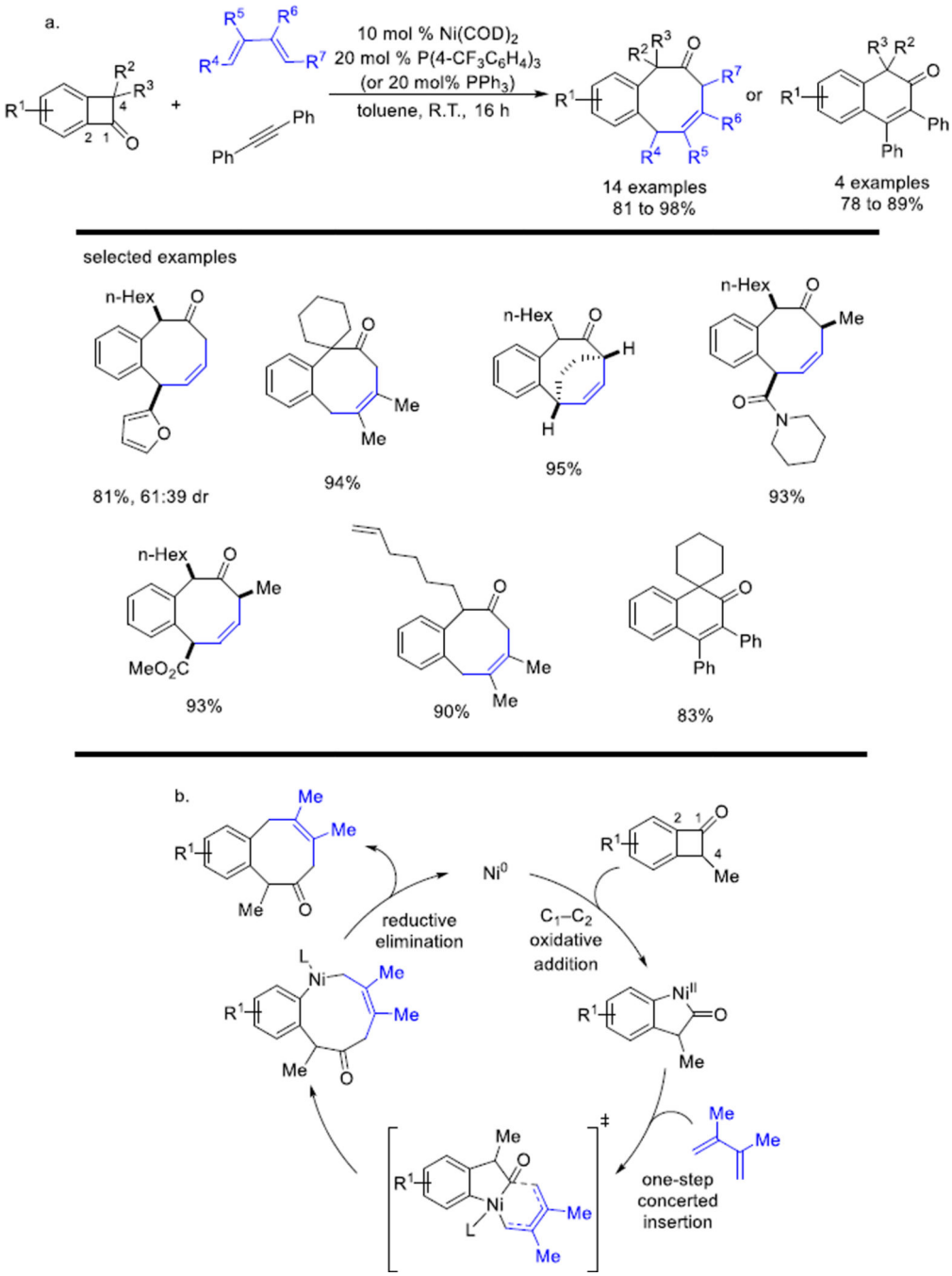



**Scheme 61.**

Enantioselective C=N bond insertion into benzocyclobutenones

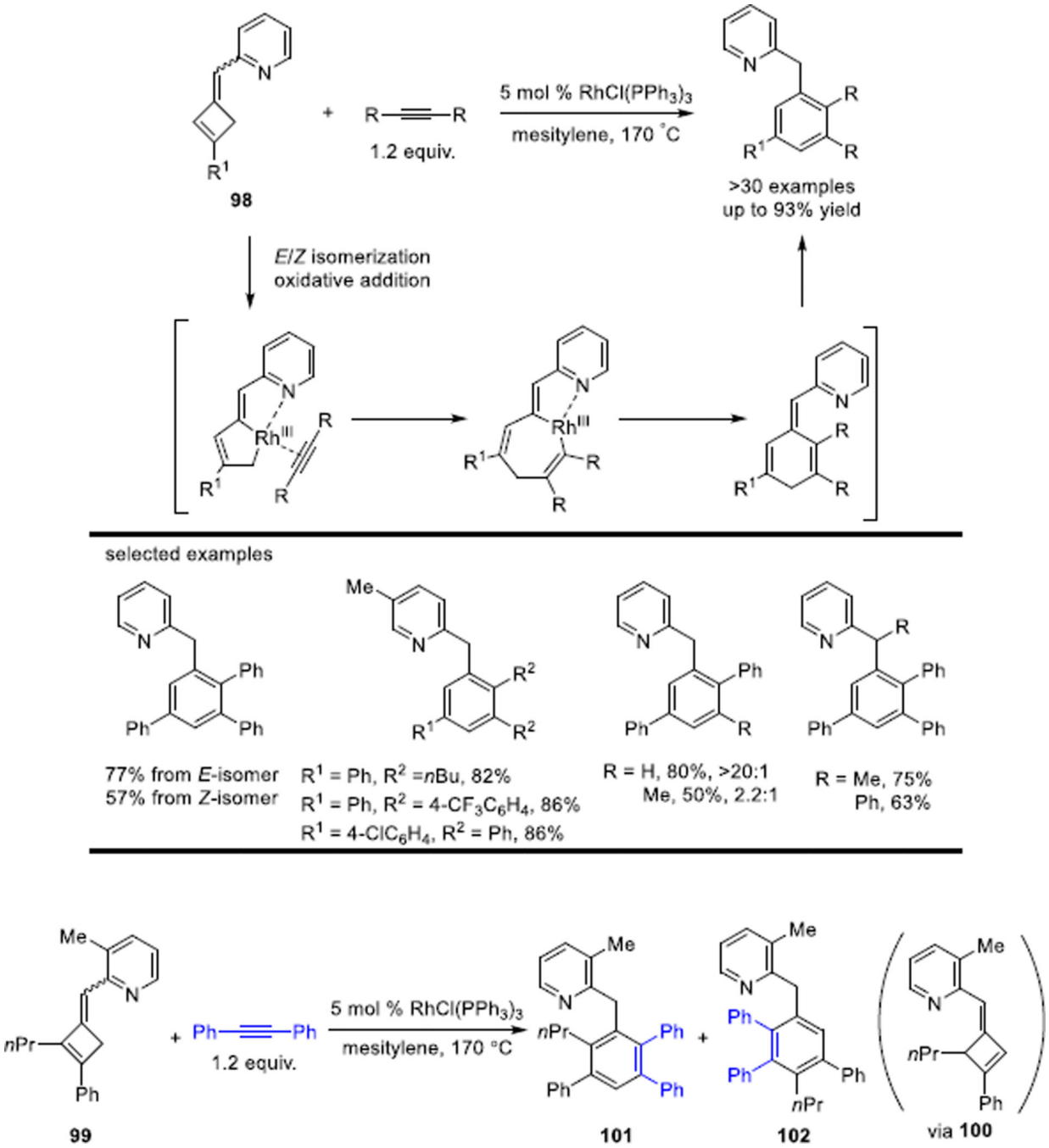



**Scheme 62.**
Diastereoselective hydrogenation of the fused scaffold



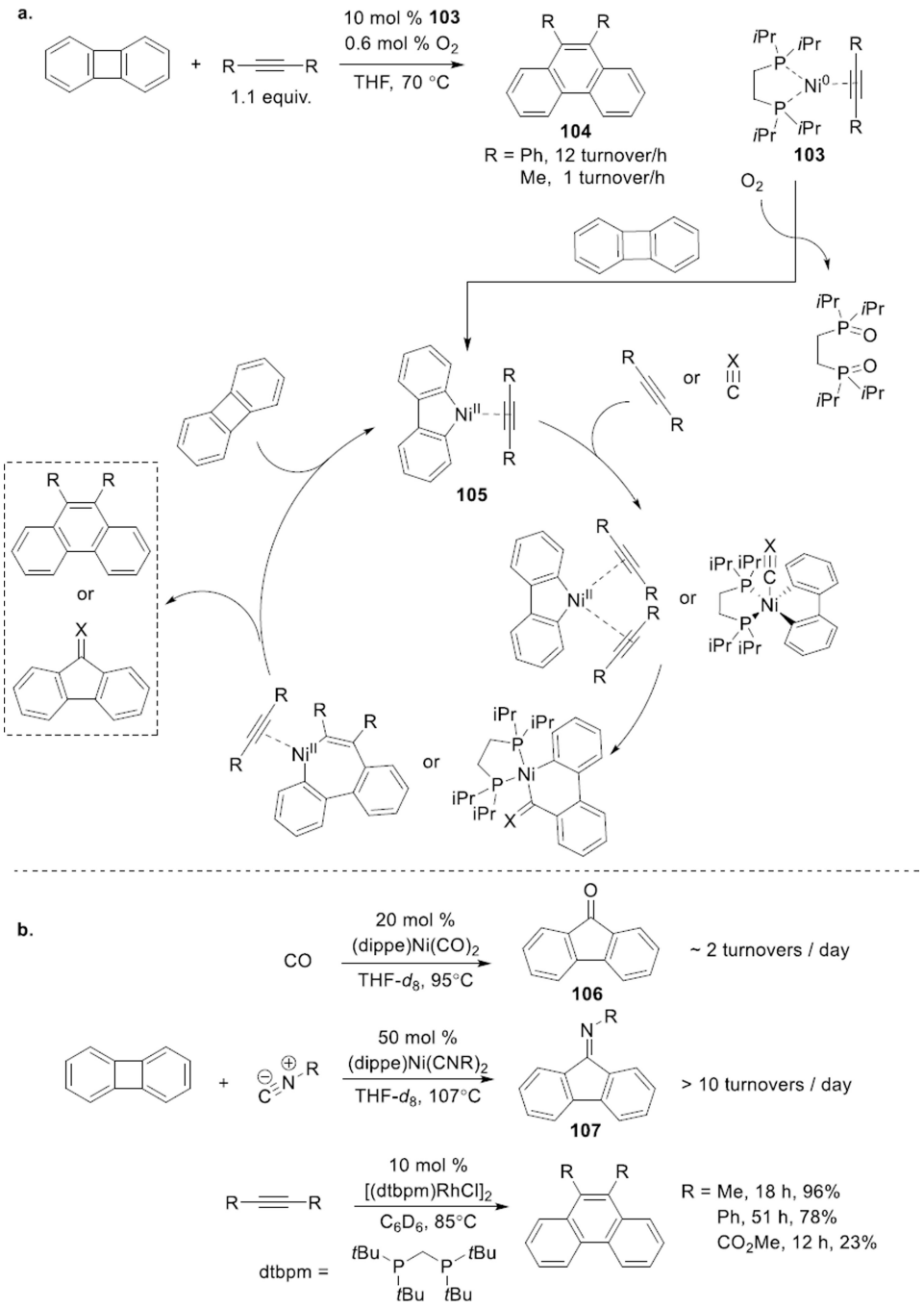

**Scheme 63.**

Intermolecular coupling of benzocyclobutenones with 1,3-dienes and acetylenes



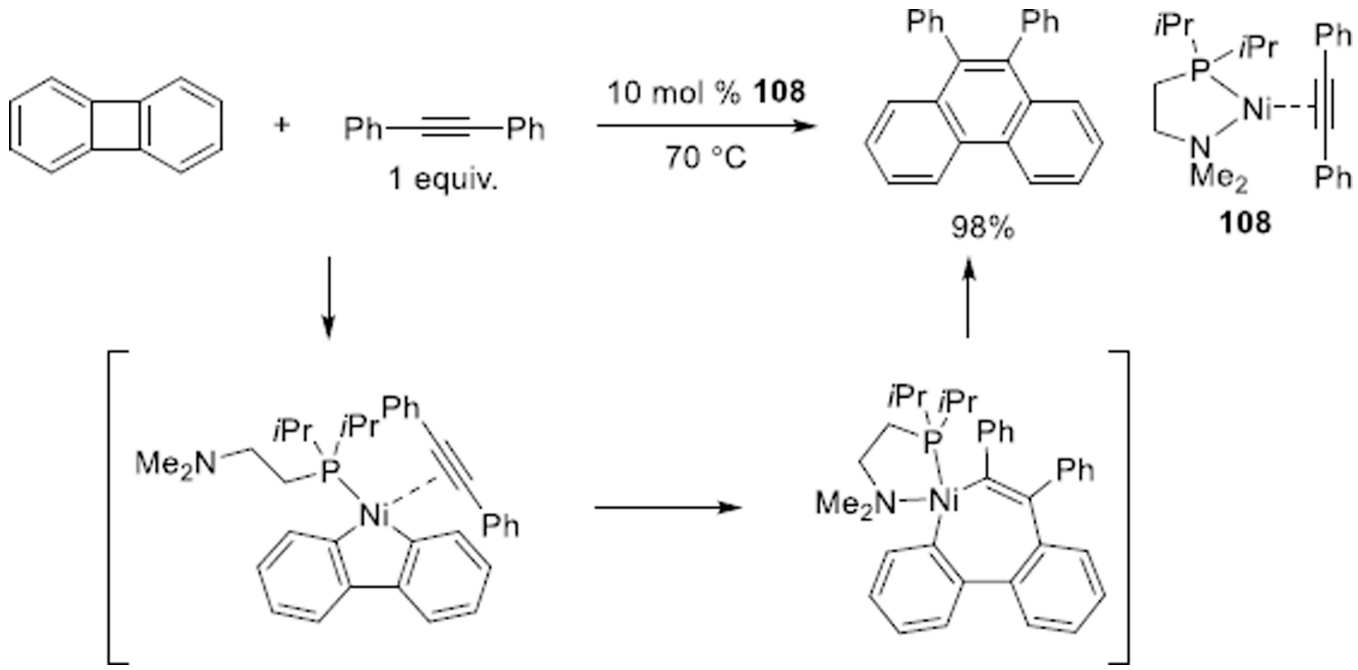

**Scheme 64.**

Rh-catalyzed coupling between methylidenecyclobutenes and alkynes

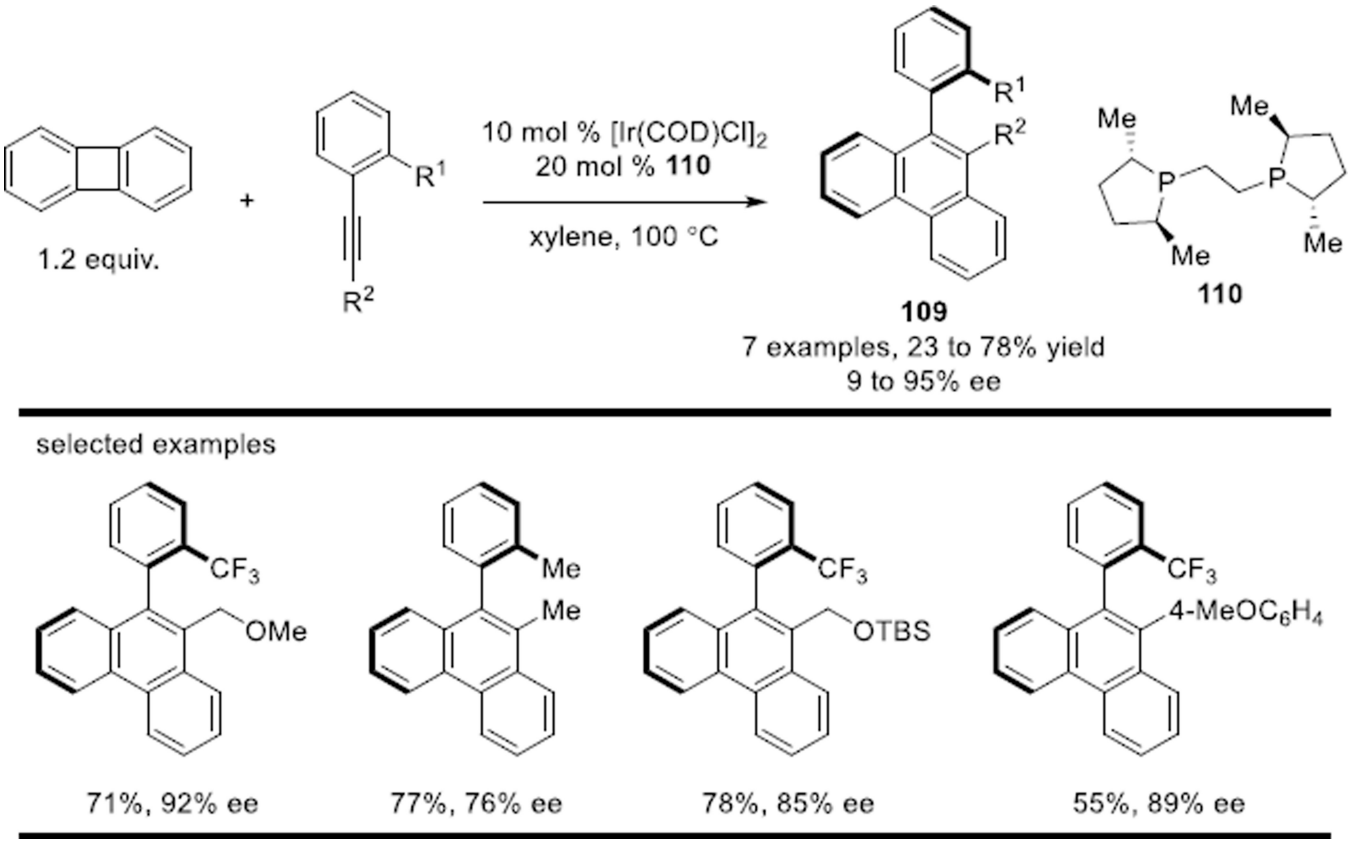



**Scheme 65.**

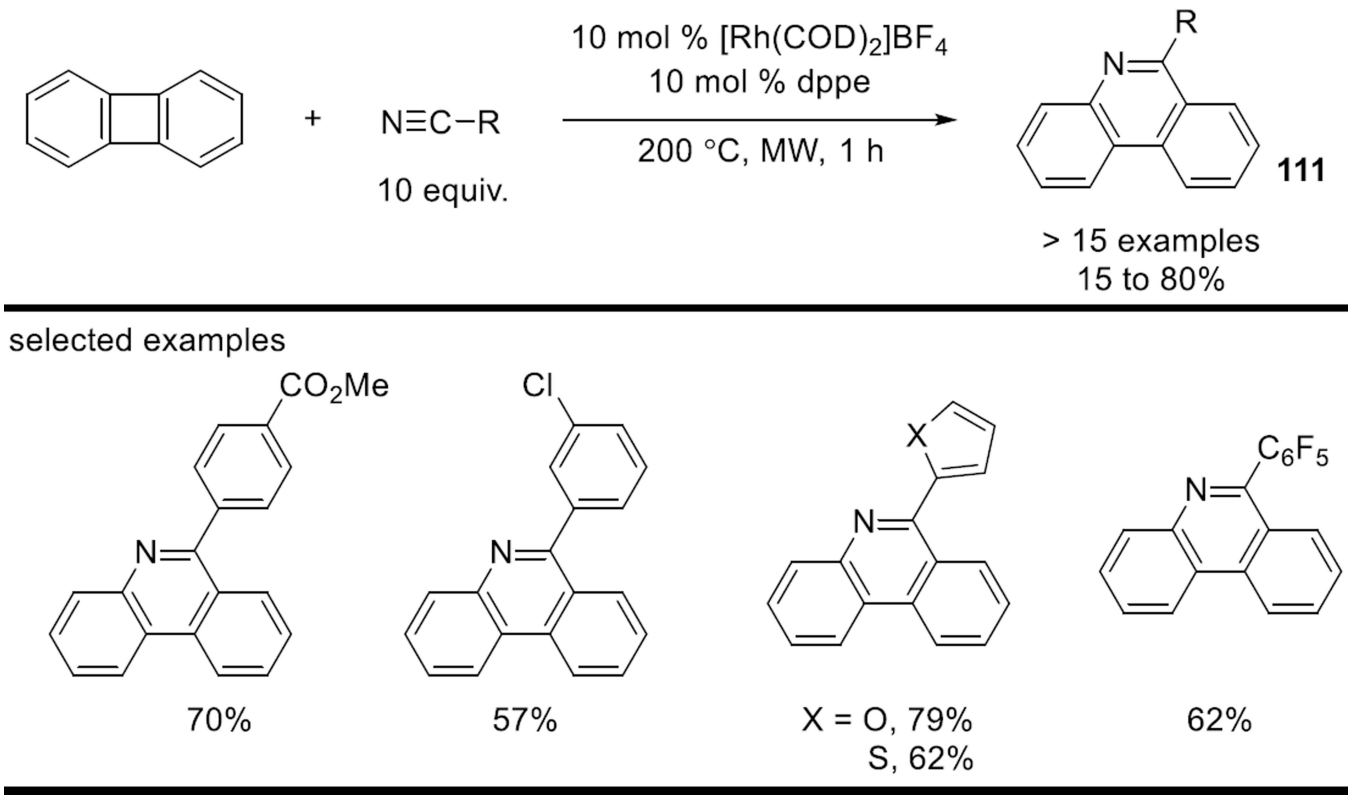
Ni-catalyzed insertion of alkynes, CO and isocyanides with biphenylenes



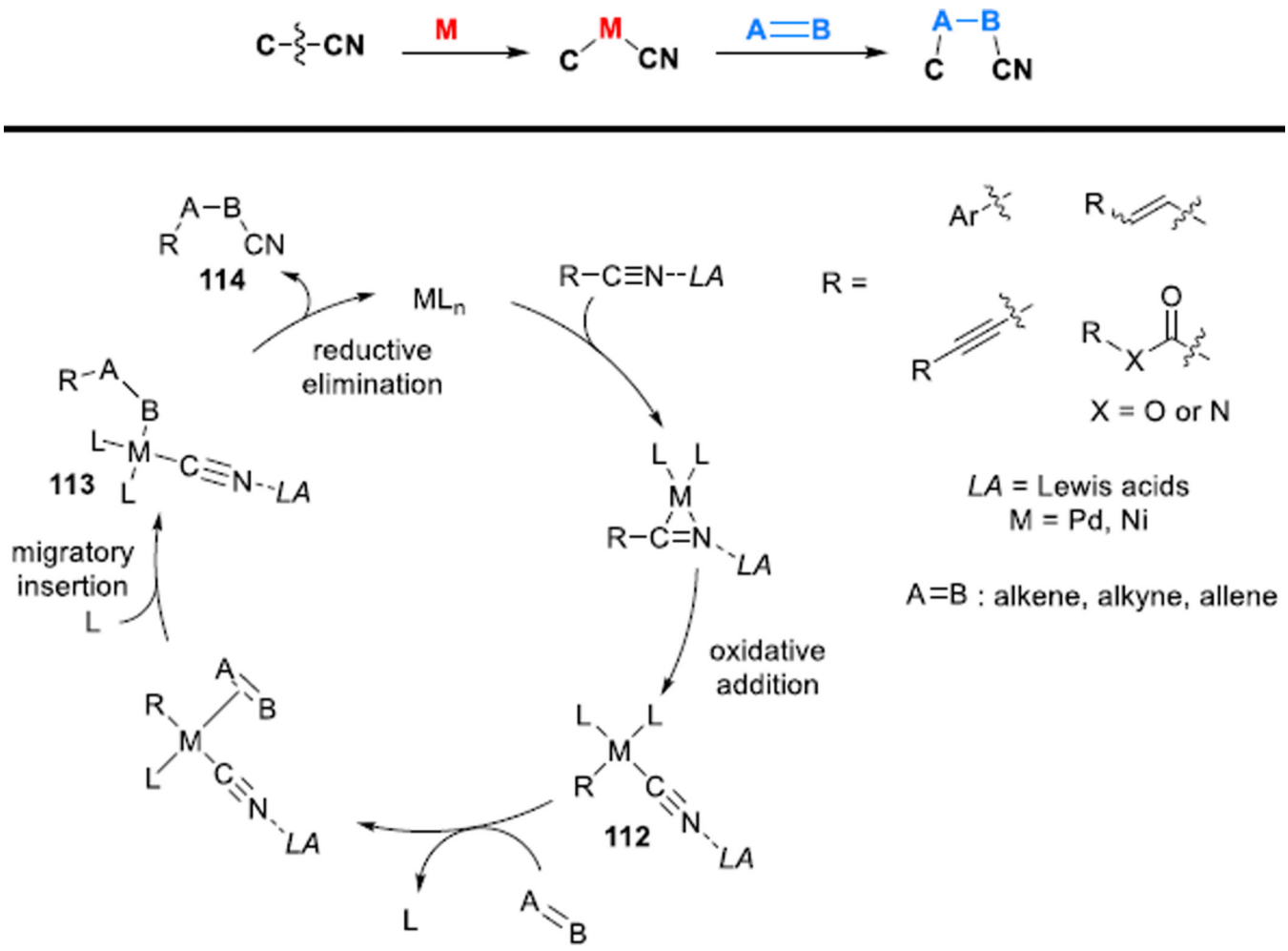

**Scheme 66.**
Using a Ni catalyst with a P,N-ligand




**Scheme 67.**
Formation of axial chirality via the “cut and sew” reaction with biphenylenes

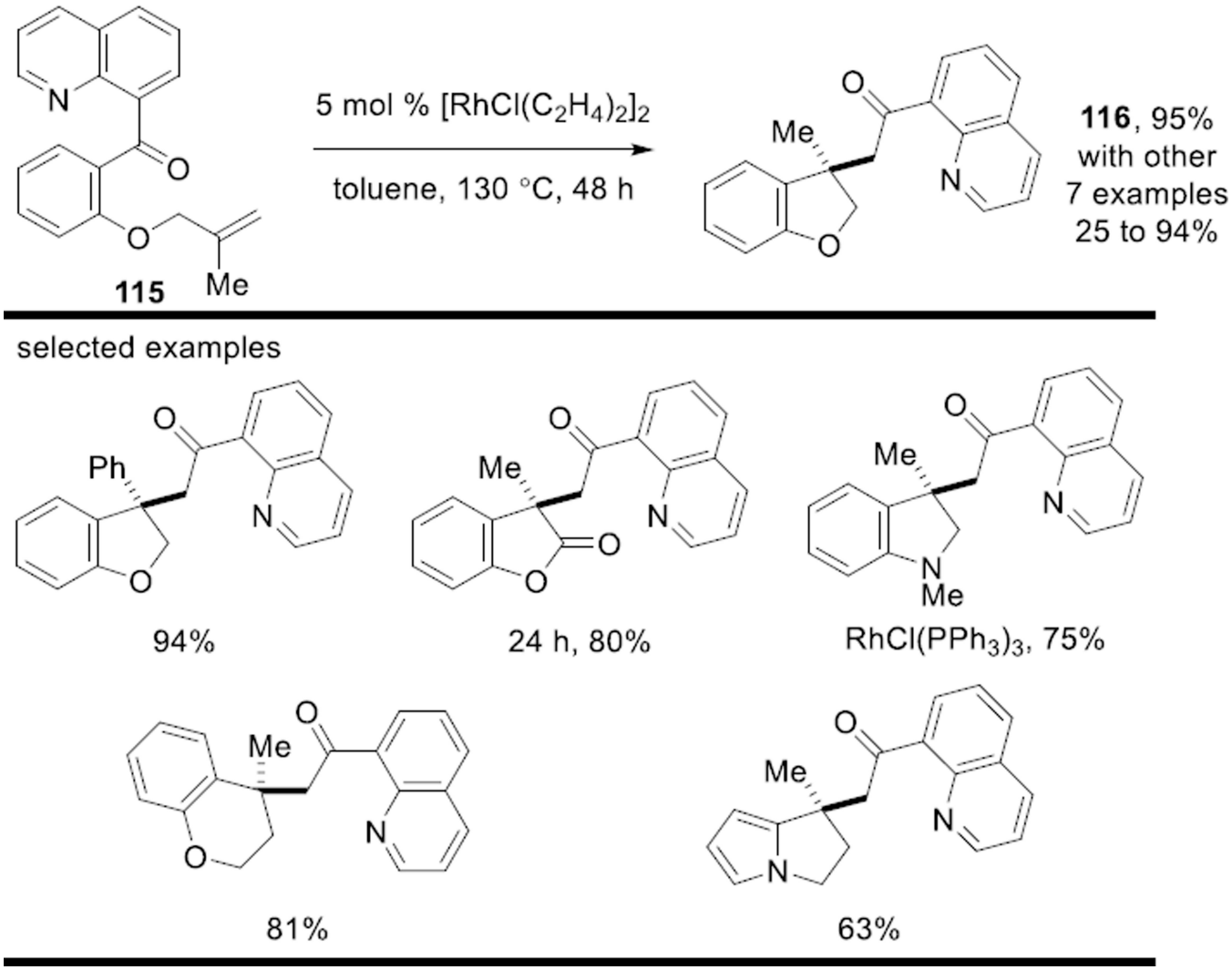



**Scheme 68.**
Coupling of biphenylenes with nitriles to form phenanthridines



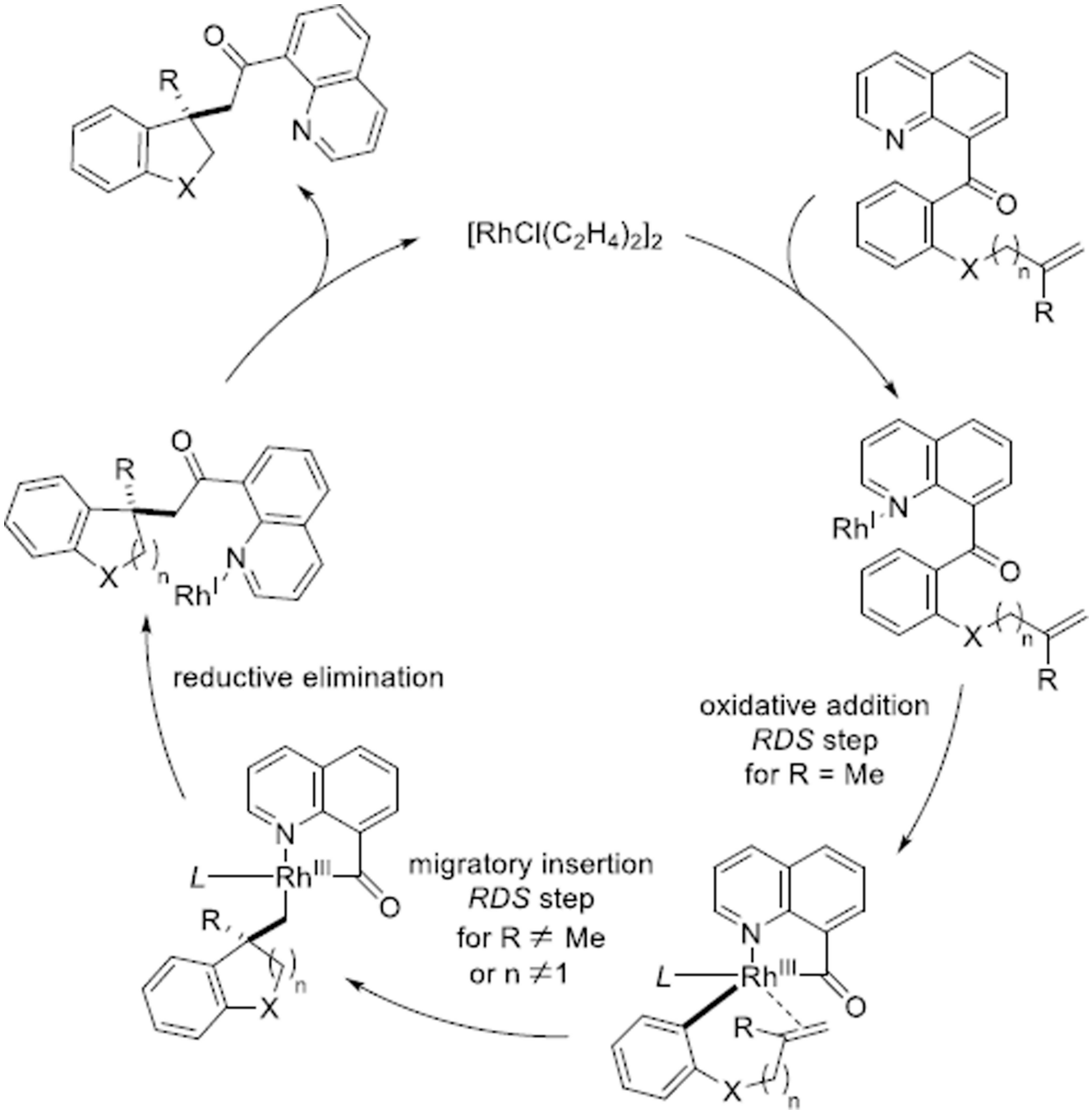

**Scheme 69.**

General mechanism for the TM-catalyzed “cut and sew” reactions via C–CN bond activation



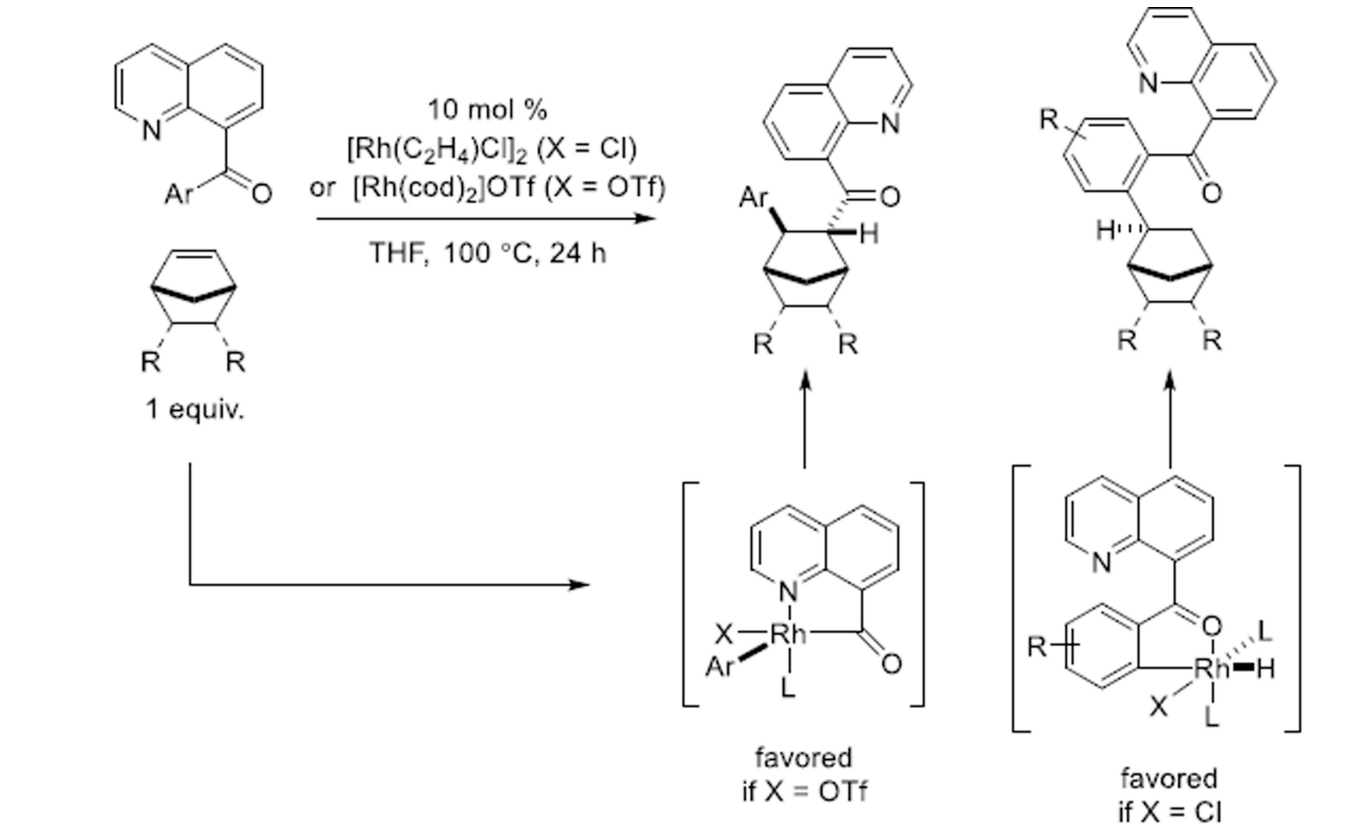

**Scheme 70.**

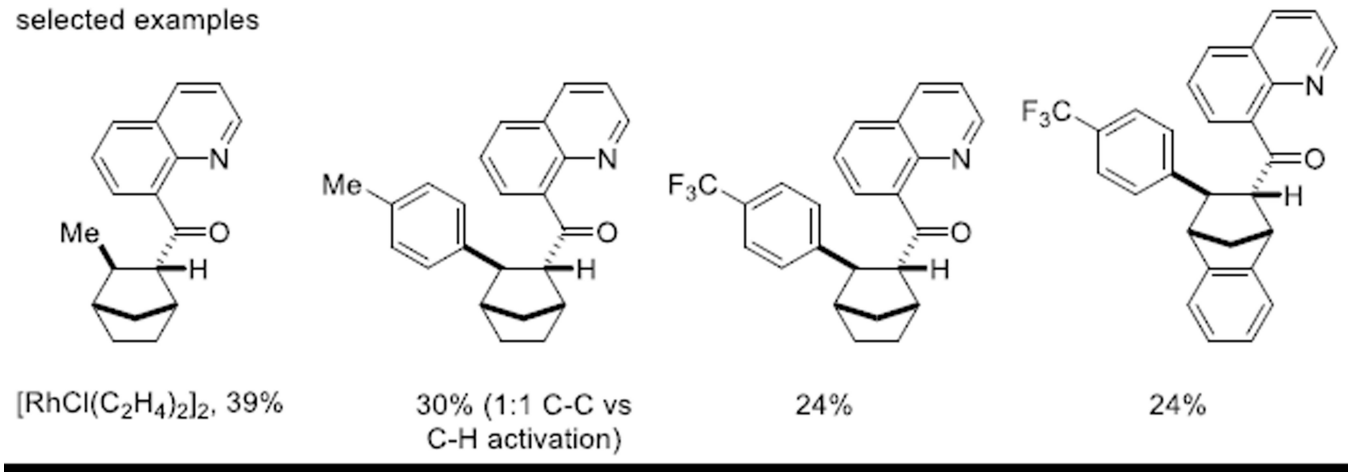
8-Quinoline-directed intramolecular carboacylation of tethered alkenes



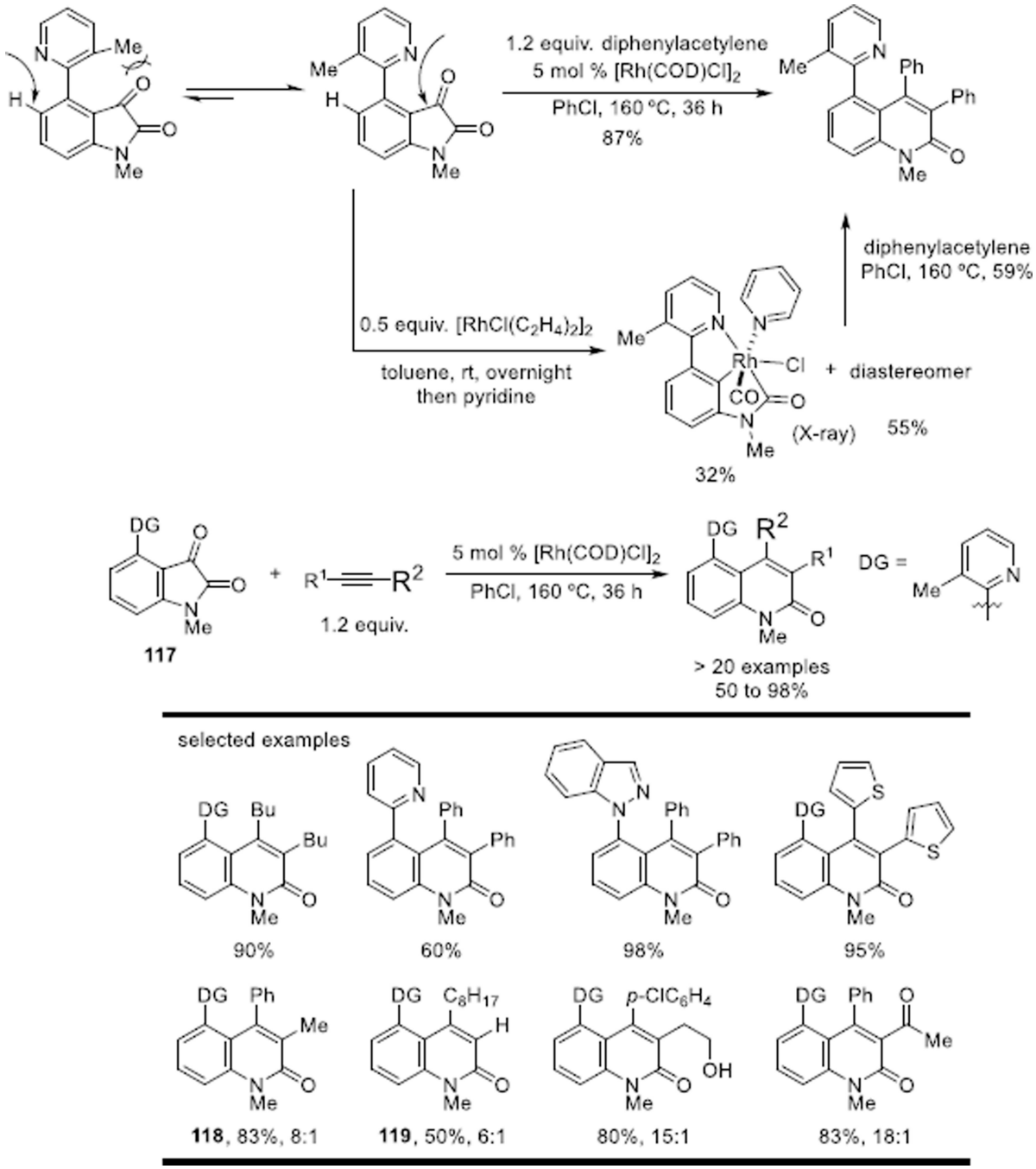

**Scheme 71.**

Proposed reaction mechanism for the 8-quinoline-directed intramolecular carboacylation of tethered alkenes



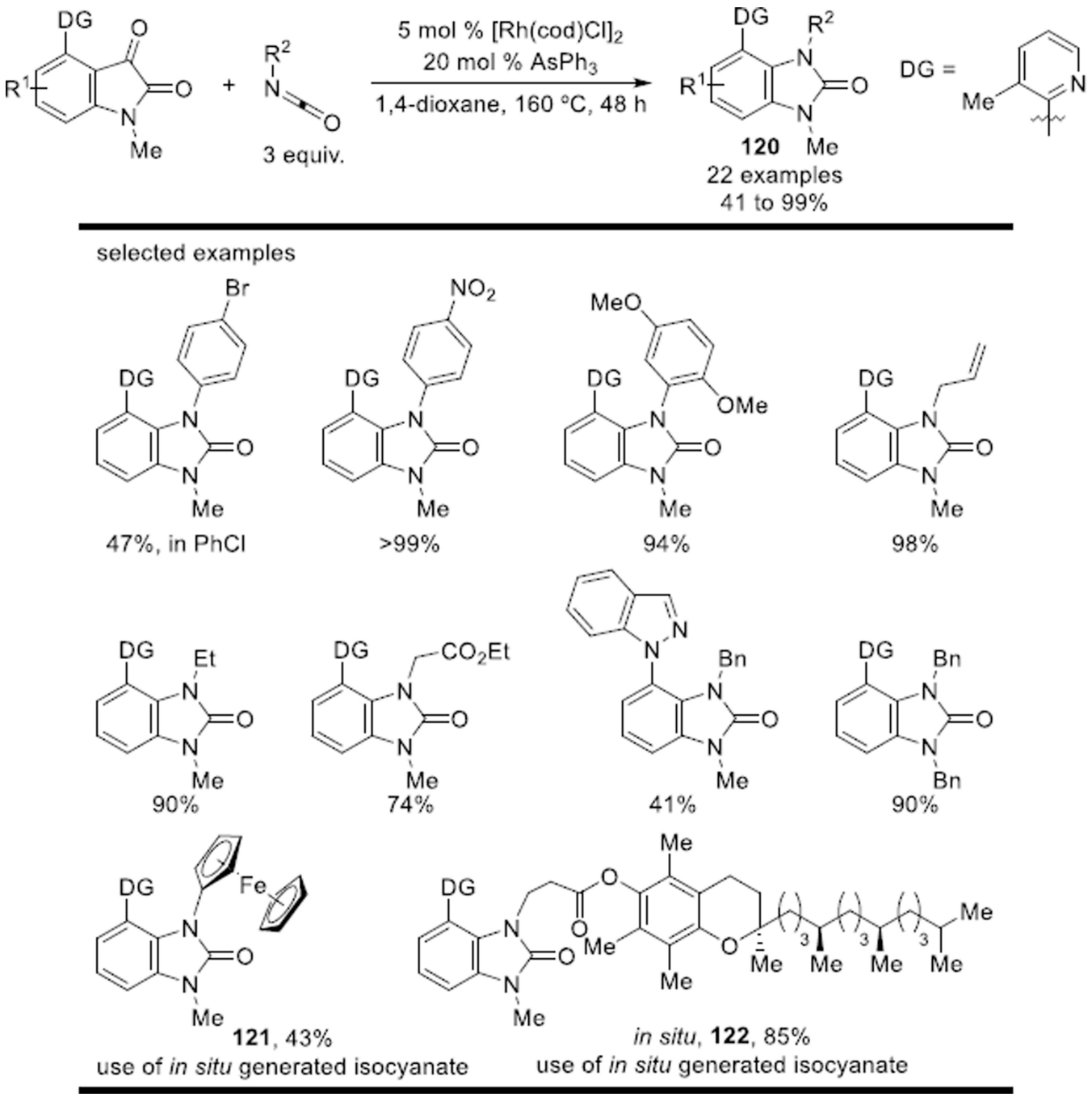




**Scheme 72.**
Directed intermolecular carboacylation of norbornene derivatives



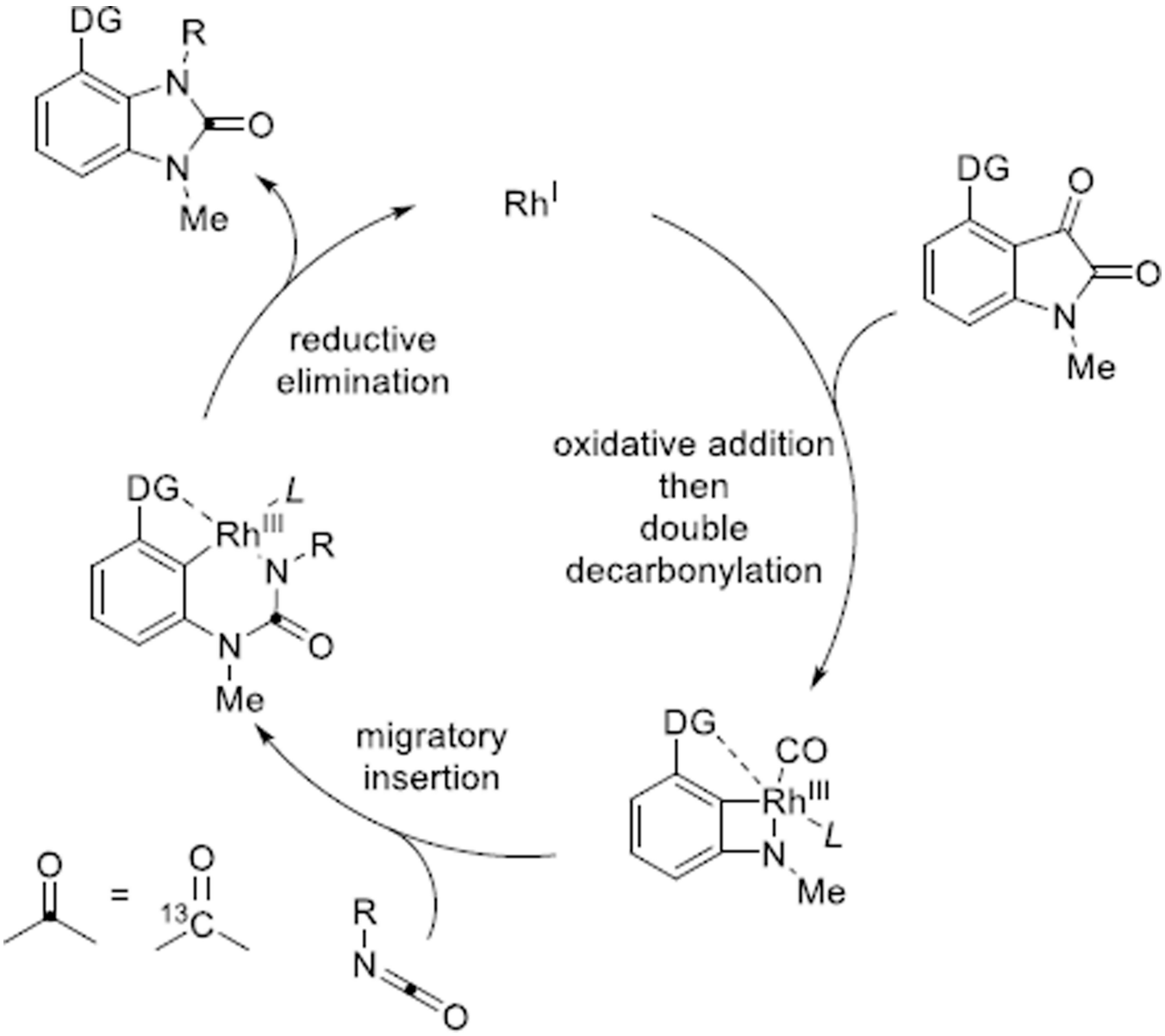

**Scheme 73.**

Directed selective C–C activation of isatins followed by decarbonylative coupling with alkynes




**Scheme 74.**

C–C activation of isatins followed by decarbonylation and coupling with isocyanates




**Scheme 75.**
Proposed mechanism for the double-decarbonylative coupling reaction