ACS Catalysis

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Transition-Metal Catalyzed Carbene Transformations *via* Ring Strain-Release Processes

Fukuan Zhang, Hui Wen, and Yaojia Jiang*

Cite This: *ACS Catal.* 2026, 16, 3013−3071 Read Online

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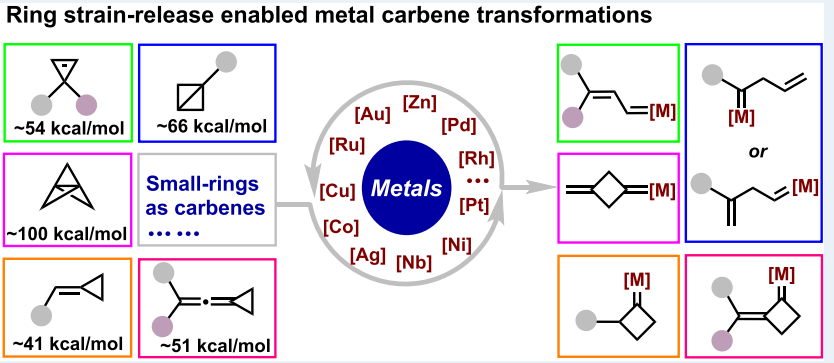

ABSTRACT: Carbenes exhibit high reactivity, enabling versatile molecular modifications with broad applications in pharmaceuticals, agrochemicals and biological chemistry. Diazo compounds have historically served as the one of the most widely applicable precursors for carbene transformations, however, they are limited by inherent instability and explosiveness. In recent years, strain-release strategies involving small, high-energy carbocyclic molecules such as cyclopropenes, bicyclo[1.1.0]butanes (BCBs), [1.1.1]propellane (TCP), methylenecyclopropanes (MCPs), and vinylidenecyclopropanes (VDCPs) have emerged as promising nondiazo type carbene precursors, providing safer and more efficient routes for metal carbene transformations. These strained molecules have expanded the synthetic toolbox through ring strain-release process, enabling transformative applications in drug innovation, pesticide design and material science. This review summarizes recent advances in ring strain-enabled carbene transformations, offering a critical evaluation of current synthetic strategies while identifying unexplored opportunities.

KEYWORDS: *strain-release, carbene chemistry, metal catalysis, small rings, synthetic method*

1. INTRODUCTION

Carbenes, a class of neutral divalent carbon species, serve as versatile synthetic intermediates for constructing new carbon−carbon and carbon−heteroatom bonds.[1] Historically, their application was limited by the reliance on photolytic or extreme thermal conditions to generate highly reactive, transient free carbenes. This approach frequently resulted in poor control over reactivity, low selectivity, and notable safety concerns (Figure 1, **A**).[2] A cornerstone breakthrough occurred with the advent of transition metal catalysis, which enabled the *in situ* generation of metal-stabilized carbene intermediates (carbenoids) from suitable precursors.[3] This strategy not only enhanced safety and controllability but also transformed carbenes into tunable synthons with predictable reactivity and stereochemical outcomes.[4] Through coordination, the metal center directs both the trajectory and spatial arrangement of the carbene, facilitating highly efficient and selective transformations such as C−H and X−H insertions, cyclopropanations, ylide formation and rearrangement etc. (Figure 1, **B**).[5] The incorporation of chiral ligands further enables exceptional enantiocontrol, offering robust routes to chiral scaffolds.[6] Moreover, transition metal catalysis has unlocked multicomponent and cascade processes, exemplified by palladium-catalyzed carbene cross-coupling, significantly expanding the synthetic toolkit for complex molecule assembly.[7]

Despite these advances, the field remains constrained by its reliance on diazo-based carbene precursors, which suffer from intrinsic instability, safety hazards, and limited functional group tolerance (Figure 1, **C**). These issues often impede precise regio- and stereocontrol in complex settings. Recent efforts to overcome these limitations have progressed along

Received: December 17, 2025
Revised: January 28, 2026
Accepted: January 30, 2026
Published: February 9, 2026

https://doi.org/10.1021/acscatal.5c09031
ACS Catal. 2026, 16, 3013−3071

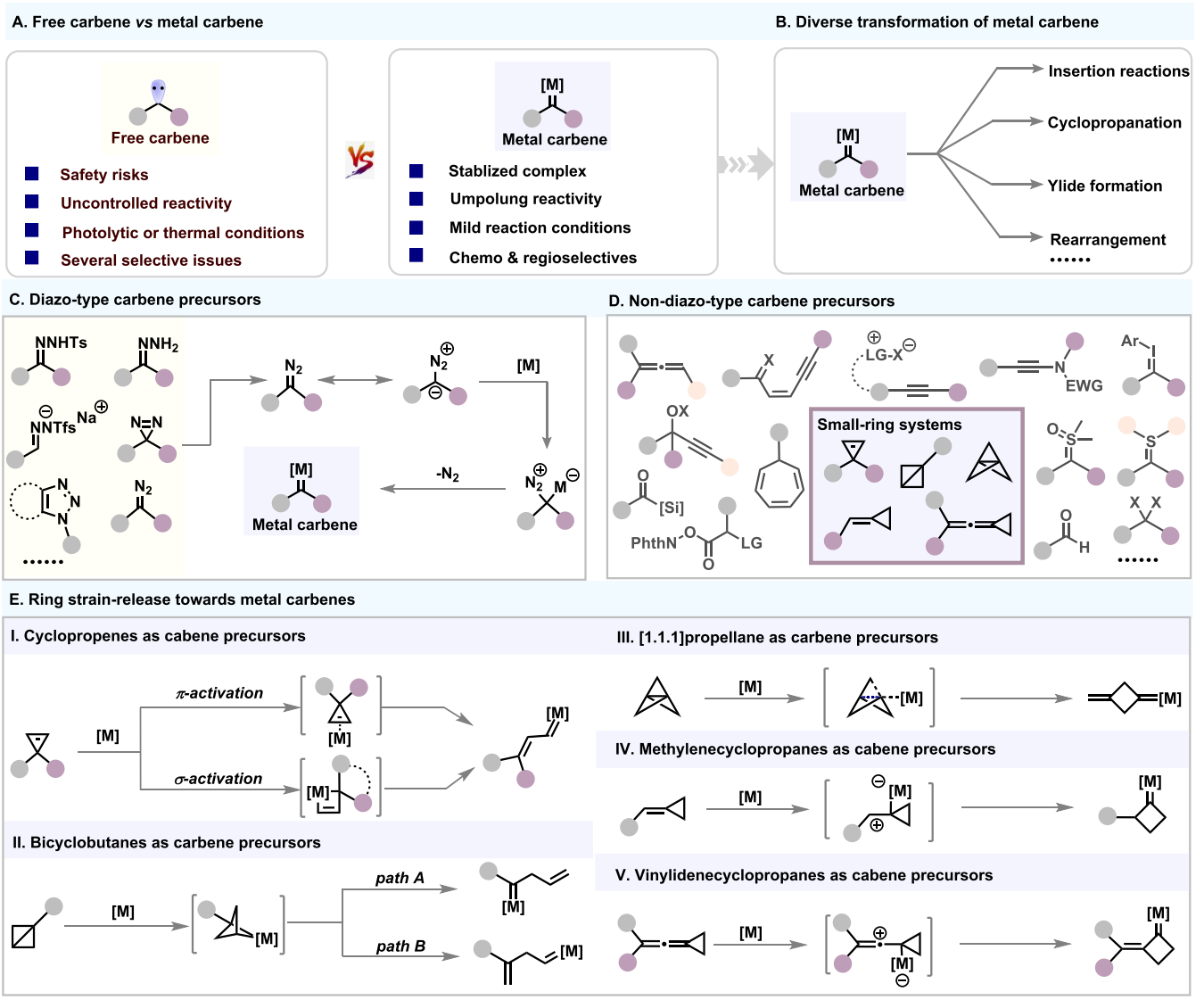

Figure 1. Background of carbene chemistry. (A) The property of free carbene and metal carbene; (B) Diverse transformation of metal carbene; (C) Diazo-type carbene precursors toward metal carbenes; (D) Nondiazo-type carbene precursors; (E) Ring strain-release toward metal carbenes.

two complementary fronts: the development of stabilized diazo-type surrogates (e.g., triftosylhydrazones) that release diazo species under mild conditions,[8] and the emergence of nondiazo carbene precursors such as allenes, ene-yne-ketones, alkynes, propargyl esters, sulfur ylides and etc (Figure 1, **D**).[9] The latter undergo carbene transfer *via* isomerization, migratory rearrangement, retro-Büchner reactions, or elimination under metal, photochemical, or thermal activation. More recently, ring strain has been harnessed as an intrinsic driving force for carbene generation. The controlled ring-opening of strained small rings under transition metal catalysis releases reactive carbenoid species under mild, safe conditions without gaseous byproducts, offering enhanced functional group compatibility and operational simplicity.[10]

In recent decades, a prominent class of strain-release carbene precursors, including cyclopropenes, bicyclo[1.1.0]-butanes (BCBs), [1.1.1]propellane (TCP), methylenecyclo-propanes (MCPs), and vinylidenecyclopropanes (VDCPs), has attracted sustained research interest (Figure 1, **E**). Cyclopropenes (≈54 kcal/mol) undergo metal-catalyzed ring opening to form donor−donor metallocarbenes, enabling C−H insertion, cyclopropanation, and heterocycle formation under mild reaction conditions. Their tunable substituents allow precise modulation of carbene electronic and steric properties.[11] The central C−C σ-bond in strained BCBs (≈66 kcal/mol) cleaves under thermal, photochemical, or metal-catalytic conditions, producing reactive carbene or radical intermediates. These species readily participate in cascade cyclizations, C−H functionalization, and cross-coupling to access bicyclic alkanes, cyclobutanes, and cyclobutenes.[12] More recently, TCP-one of the most strained carbocycles known (≈100 kcal/mol)-has emerged as a potent carbene precursor. Its bridge C−C bonds can be selectively activated under mild conditions, generating intermediates that facilitate the construction of bridged polycyclic 3D architectures and enable concerted radical/carbene trans-formations. TCP thus offer new avenues to pharmacologically relevant scaffolds, polymer monomers, and functional materials.[13] Methylenecyclopropanes (MCPs), comprising a strained cyclopropane ring fused to an exocyclic alkene, have

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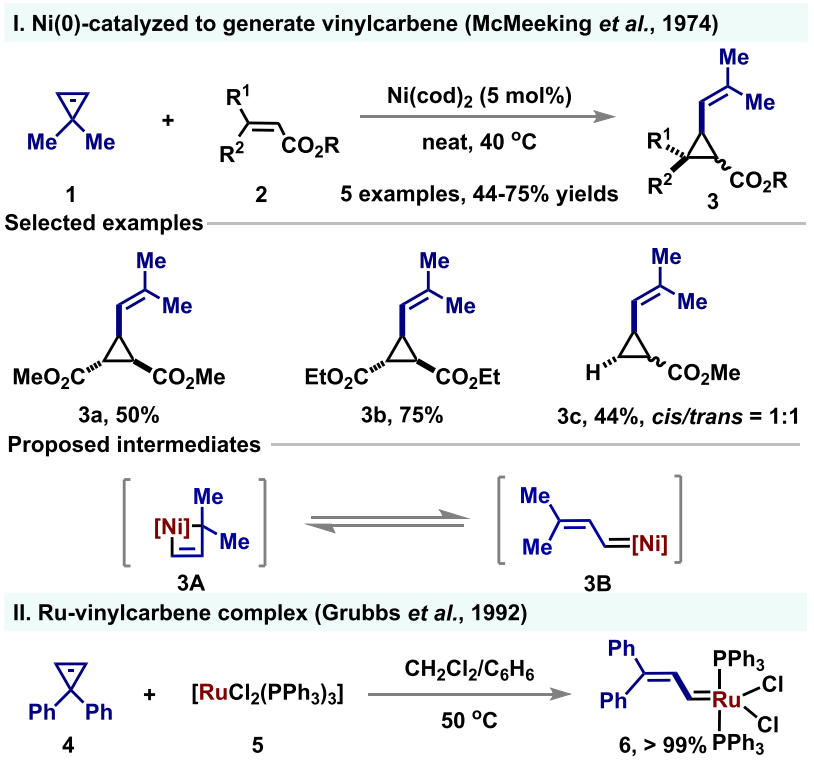
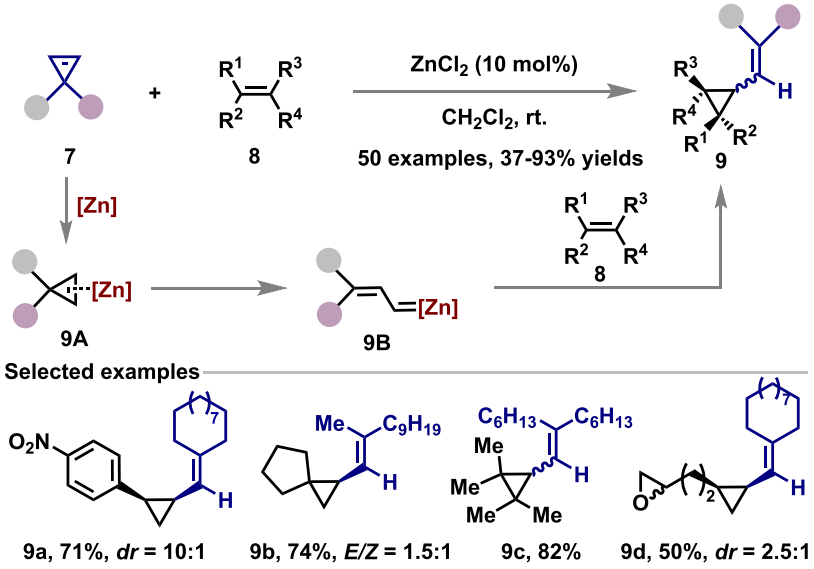
Scheme 1. Pioneer Works of Cyclopropenes as Carbene Precursors



Scheme 2. Zn-Catalyzed Ring-Opening of Cyclopropenes as Carbene Precursors



attracted substantial attention due to their synthetic accessibility and diverse reactivity.[14] The inherent ring strain of cyclopropane (≈40.9 kcal/mol) and the olefinic character of the exocyclic double bond allow MCPs to undergo a variety of ring opening transformations under transition metal catalysis, establishing them as versatile C_4 synthons.[15] Vinylidenecyclopropanes (VDCPs)—structurally related to MCPs—feature an allene unit directly attached to a strained cyclopropane ring, with a ring strain of approximately 50.9 kcal/mol.[16] Their high strain energy and unique molecular topology have positioned VDCPs as valuable multicarbon synthons in organic synthesis.[17]

Several reviews have already summarized the property and reactivity of these unique strained systems.[18] For instance, the chemistry of cyclopropenes—including carbene transfer reactions—was comprehensively summarized by Vicente covering the period from 2007 to 2019.[18a] In addition, recent contributions by Feng,[18b] Sodano,[18c] and others have highlighted the synthetic utility of BCBs from multiple perspectives. Despite these efforts, a systematic overview dedicated specifically to carbene generation and transformation enabled by strain release from small-ring systems is still lacking. This review aims to address this gap by providing a focused account of recent progress in carbene

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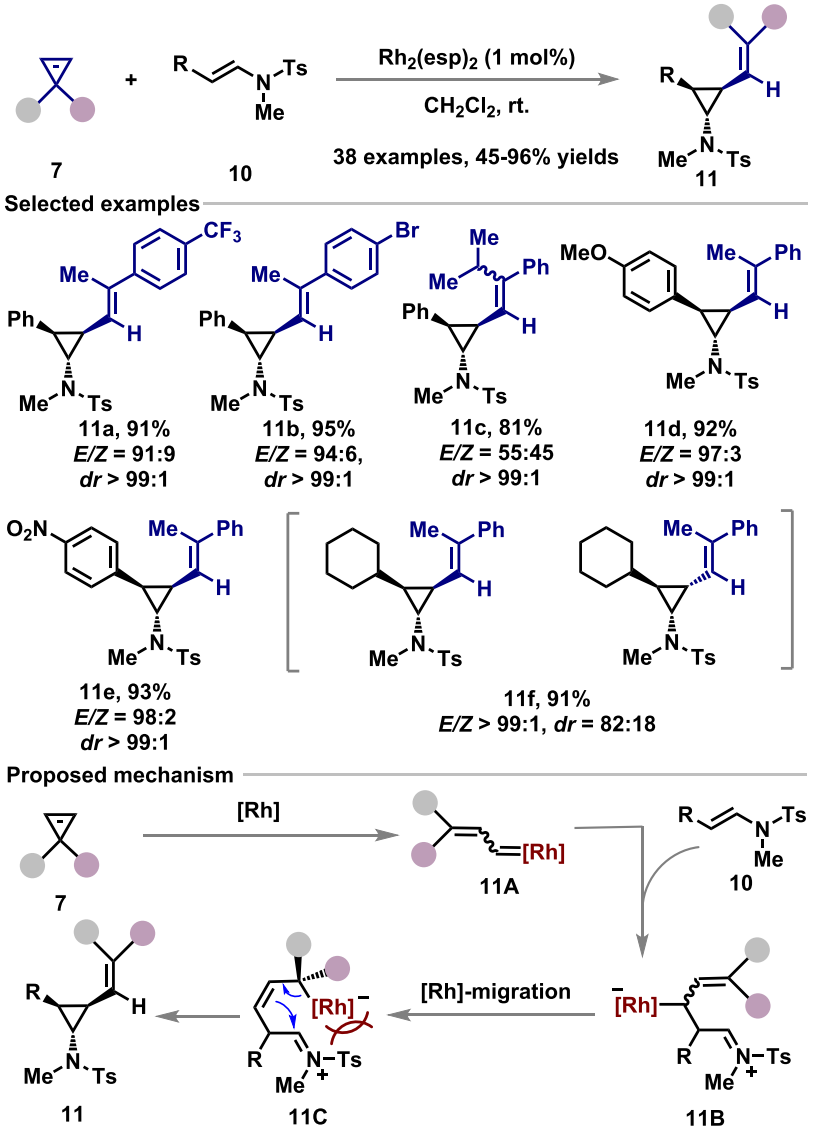
Scheme 3. Stereoselective Cyclopropanation of *N*-Ts Enamines



chemistry driven by the strain-release strategy. We will systematically examine molecular design principles, the electronic and structural characteristics of the resulting carbene intermediates, and underlying reaction mechanisms, with emphasis on three representative scaffolds—cyclopropenes, BCBs, and TCP—as well as other interesting small-ring carbene precursors. Key challenges, such as selectivity control and functional group compatibility, will be critically evaluated and discussed. Furthermore, we will outline future directions and potential applications across agricultures, medicinal chemistry and materials science.

2. STRAIN-RELEASE RING OPENING OF CYCLOPROPENES TO GENERATE VINYLCARBENES

Cyclopropene, the smallest cyclic alkene characterized by a C=C bond, derives its distinctive reactivity from substantial ring strain, establishing itself as a privileged scaffold in modern organic synthesis.[19] The inaugural synthesis and isolation of cyclopropene by Doyarenko and co-workers in 1922 marked the beginning of a rich exploration into its chemical behavior.[20] Initially studied for its unique olefinic properties,[21] cyclopropene has more recently emerged as a versatile precursor to vinyl metal carbene intermediates under transition metal catalysis, substantially expanding its utility in complex molecule synthesis.[11]

A pivotal early contribution was made by McMeeking et al. in 1974, who demonstrated that 3,3-dimethylcyclopropene **1** undergoes bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$)-catalyzed reaction with electron-deficient alkenes **2** to afford stereoselective cyclopropanation products **3** (Scheme 1, **I**).[22] As cyclopropanation serves as a diagnostic transformation for carbene involvement, the authors proposed initial Ni(0) coordination to the cyclopropene (intermediate **3A**), followed by C−C bond cleavage to generate a transient vinyl nickel carbene species **3B**. Direct experimental validation of such intermediates remained elusive until Grubbs and co-workers reported in 1992 the synthesis and structural characterization of a stable ruthenium vinyl carbene complex **6** from cyclopropene **4** and dichlorotris(triphenylphosphine)-ruthenium $[RuCl_2(PPh_3)_3]$ **5**, providing unequivocal evidence for the metallocarbene pathway (Scheme 1, **II**).[23] Subsequent mechanistic insights into the metal-mediated ring-opening of cyclopropenes have stimulated the design of diverse cyclopropene derivatives and catalytic systems, fostering the

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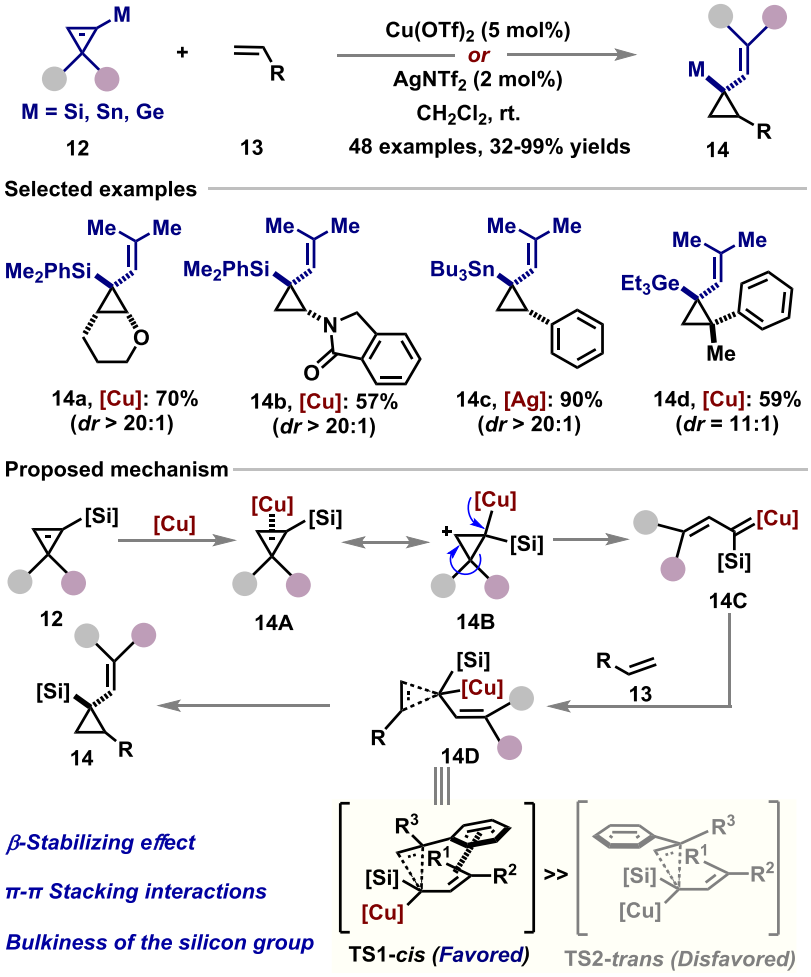
Scheme 4. Cyclopropanation of Silyl-, Germanyl- and Stannyl Vinylcarbenes with Styrenes



development of an extensive toolbox of carbene-based transformations.

Contemporary applications of cyclopropene derivatives now encompass not only classical carbene reactions—including cyclopropanation,[11d] insertion processes,[24] ylide formation[25] and cycloadditions[18a]—but also more recently developed coupling reactions,[26] rearrangements,[27] isomerizations[28] and etc. Building upon the comprehensive coverage of cyclopropene chemistry by Vicente through 2020,[18a] this section focuses specifically on advances since 2020 in the context of cyclopropenes as carbene precursors, with appropriate references to foundational work where necessary for clarity and continuity.

2.1. Cyclopropanation of C=C Bonds with Vinylcarbenoids

Cyclopropane represents the smallest all-carbon ring system, characterized by a substantial ring strain of approximately 29.0 kcal/mol.[29] This inherent strain energy has been strategically harnessed to drive a wide array of transformations in organic synthesis. Beyond exhibiting olefin-like reactivity, cyclopropanes serve as versatile three-carbon synthons for the assembly of complex molecular architectures.[30] In medicinal chemistry, the cyclopropane motif is recognized as a privileged scaffold, conferring improved physicochemical properties—such as enhanced metabolic stability and membrane permeability—with a negligible increase in molecular weight.[31] This scaffold is not only embedded in the core of numerous natural products but also prevalent in marketed drugs.[32] Its utility in bioactive molecule design is further underscored by recent agrochemicals including cyclaniliprole and afidopyropen, which incorporate the cyclopropane architecture.[33] Moreover, the cyclopropane ring confers precise spatial rigidity and well-defined three-dimensional orientation, properties that have enabled its application in materials science.[34] Consequently, the development of efficient and streamlined methodologies for accessing multifunctionalized cyclopropanes remains a significant objective.[35]

Cyclopropene has emerged as a highly versatile building block that offers more direct and efficient routes to cyclopropane frameworks.[36] The direct functionalization of the endocyclic C=C double bond in cyclopropenes provides straightforward access to cyclopropane derivatives.[37] On the other hand, cyclopropenes can function as vinyl carbene precursors, engaging in cyclopropanation reactions with alkenes to deliver vinylcyclopropanes with high efficiency.[18a] As one of the most emblematic transformations in carbene chemistry, cyclopropanation stands as the premier strategy for cyclopropane ring construction.[38] While diazo compounds bearing electron-withdrawing groups are widely employed as carbene precursors,[39] donor−donor-type vinyl diazo species are often hampered by poor stability, limiting their utility in the synthesis of vinyl-substituted cyclopropanes.[40] In contrast,

https://doi.org/10.1021/acscatal.5c09031
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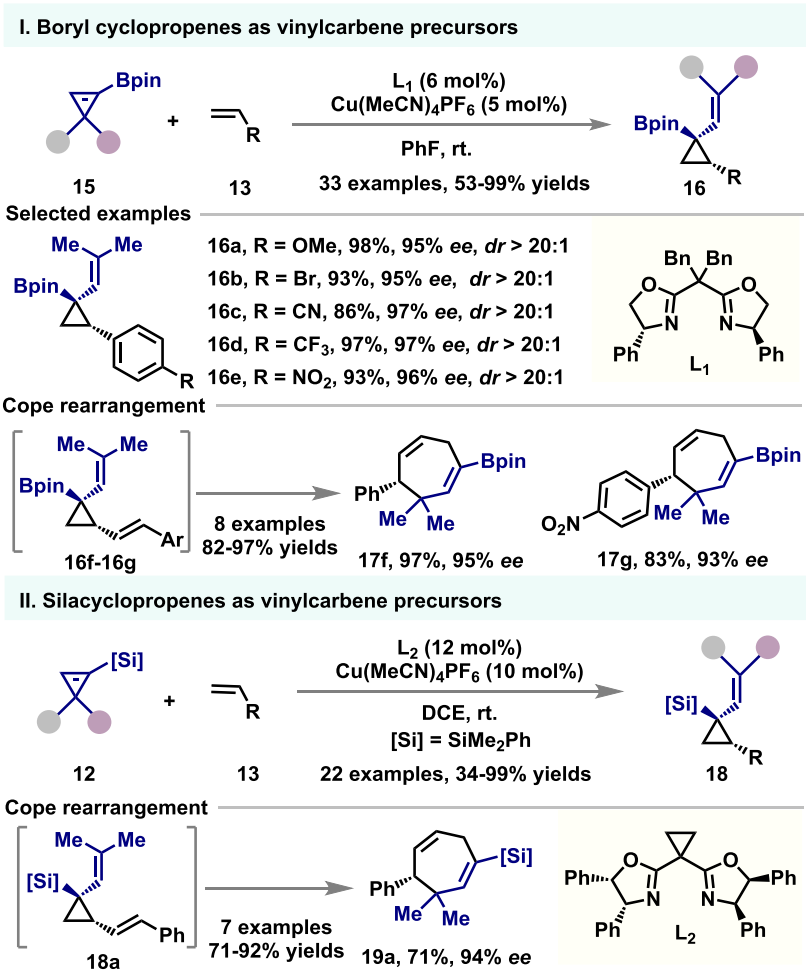
Scheme 5. Asymmetric Cyclopropanation of Boryl- and Silyl- Vinylcarbenes with Styrenes



transition-metal-catalyzed activation of cyclopropenes enables direct generation of vinyl carbene intermediates—either unsubstituted or bearing specific substituents (e.g., Si, B, Sn) at the α-position—thus opening new avenues to polysubstituted vinylcyclopropanes.[41]

The transition metals that promote the ring-opening of cyclopropenes to form vinyl carbene metal complexes are predominantly precious metals, such as Rh(II), Ru(II), and Au(I).[42] The use of earth-abundant metals to promote this transformation was unreported until 2015, when Vicente and co-workers demonstrated that a simple zinc salt could catalyze the ring-opening of cyclopropene **7** to generate a vinyl zinc carbene complex **9B**.[43] This intermediate participates in efficient cyclopropanation with a range of linear alkenes **8**, affording vinylcyclopropane products **9** (Scheme 2). The reaction tolerates variously substituted styrenes, unactivated alkenes, cyclic and acyclic 1,2-disubstituted alkenes, and even polyene substrates. Impressively, epoxide functionalities—which are typically sensitive to Lewis acids—remain intact under the reaction conditions, as evidenced by the formation of product **9d**. Despite its broad scope, the method encounters challenges in stereocontrol, particularly when unsymmetrical 3,3-disubstituted cyclopropenes are employed as vinyl carbene precursors with low E/Z selectivity **9b**.

A long-standing challenge associated with the use of cyclopropenes as carbene precursors has been the control over E/Z stereoselectivity of the alkene formed after ring-opening. In 2022, the Jiang group disclosed a rhodium-catalyzed ring-opening of 3,3-disubstituted cyclopropene **7**, which generates a vinyl rhodium carbene species that undergoes cyclopropanation with enamine substrate **10**, enabling the highly stereoselective construction of vinylcyclopropylamides **11** (Scheme 3).[44] Through precise design of the alkene substrate—specifically, the introduction of an *N*-tosyl (Ts) group—the reaction achieves control over both diastereo- and E/Z-selectivities, governed by the combined electronic and steric effects of the Ts group. Substrate electronic properties showed no significant impact on reaction efficiency (**11a**–**11b**). In contrast, alkyl-substituted cyclopropene substrates, influenced by steric effects, led to relatively lower E/Z selectivity **11c**. Various aryl-substituted and terminal enamine derivatives afforded high yields and stereoselectivity (**11d**–**11e**), while alkyl-substituted enamine substrates generated a mixture of diastereomers **11f**. Additional control experiments demonstrated the critical role of the *N*-Ts group in stereoselectivity control. In the proposed mechanism, bis[rhodium($\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionic acid)] ($Rh_2(esp)_2$) initially coordinates to cyclopropene **7** and isomerizes to form the rhodium carbene species **11A**.

Subsequent nucleophilic attack by the electron-rich enamine **10** on carbene **11A** generates the zwitterionic intermediate **11B**. They propose that rhodium migration

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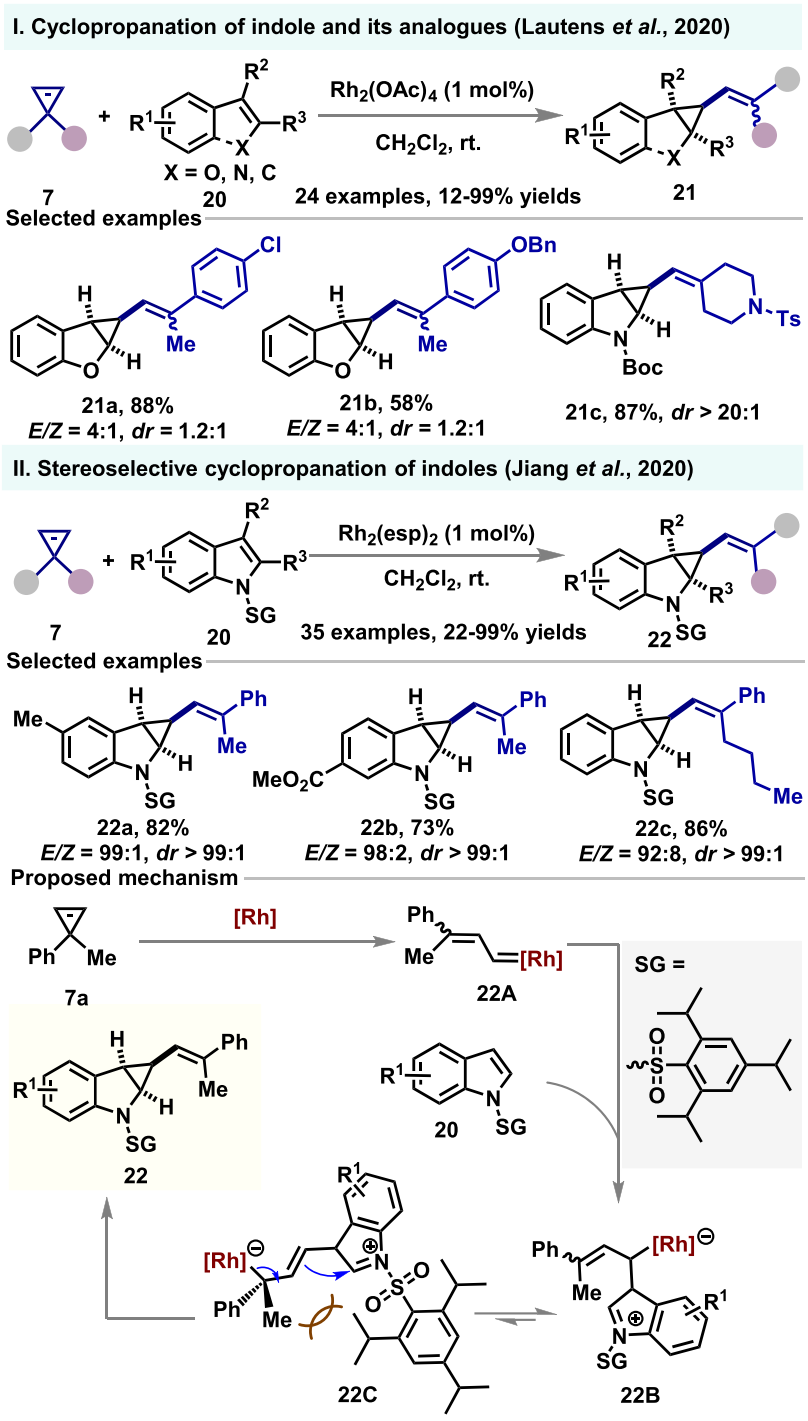
Scheme 6. Cyclopropanation of Indoles and Analogues with Cyclopropenes



from **11B** to **11C** induces isomerization of the C=C double bond to a C−C single bond, thereby enabling *E*/*Z* selectivity control through steric interactions between the rhodium catalyst and the substrate. Intermediate **11C** finally undergoes cyclization to afford the cyclopropane product **11**.

In 2022, the Vicente group reported the cyclopropanation of alkenes **13** using 1-silylcyclopropene **12** as a carbene precursor, achieving efficient construction of multifunctionalized silylcyclopropanes (Scheme 4).[41] Catalyzed by inexpensive copper(II) salts, the reaction afforded silicon-substituted cyclopropanes in good yields, establishing a new quaternary carbon center with high chemoselectivity and stereoselectivity. Notably, the reaction proceeded effectively even when employing iron salts such as iron(II) bromide ($FeBr_2$) or iron(III) bromide ($FeBr_3$) as catalysts. Beyond simple alkenes, enol ethers and enamines were also viable substrates, successfully giving the corresponding oxygen- and nitrogen-containing cyclopropane derivatives (**14a**−**14b**). Furthermore, they investigated the [2 + 1] cycloaddition of 1-stannylcyclopropene with alkenes, revealing that silver(I) bis(trifluoromethanesulfonyl)imide ($AgNTf_2$) catalysis afforded the corresponding cyclopropylstannane **14c** in 90% yield. Extending the cyclopropene scope to germanium-substituted variants under copper salt catalysis provided the

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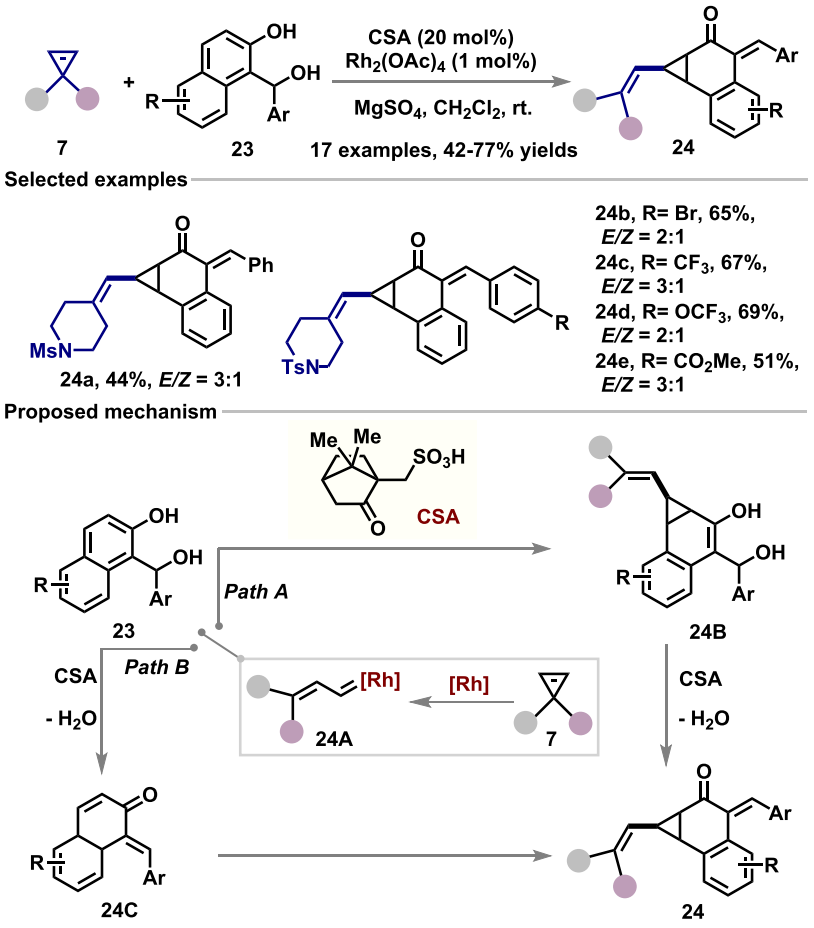
Scheme 7. Dearomative Cyclopropanation of Naphthols



target product **14d** in 59% yield with 11:1 *dr*. A proposed pathway involves initial coordination of the copper salt to the double bond of the cyclopropene **14A**, inducing selective cleavage of a C−C single bond to generate the α-silyl copper carbenoid **14C**. Subsequent cyclopropanation of the alkene by this complex may theoretically proceed through two transition states, **14D** (**TS1-*cis*** and **TS2-*trans***). Due to the steric influence of the silyl group, β-silicon stabilization effects, and $\pi-\pi$ stacking interactions between the alkene double bond and the aromatic ring, **TS1-*cis*** is spatially favored, leading to predominant formation of the *cis*-configured product **14**.

In 2024, the Zhu group reported the asymmetric cyclopropanation of alkenes with a boron-substituted cyclopropene derivative **15** (Scheme 5, **I**).[45] Through the coordination of an inexpensive copper(I) catalyst and a chiral bis(oxazoline) ligand, this boron-substituted cyclopropene efficiently generates an α-boryl vinyl carbene complex, enabling the synthesis of diverse chiral organoboron cyclopropane frameworks **16**. This strategy overcomes the stability issues inherent to traditional α-boryl diazo compounds, which arise from the strong Lewis acidity of the boryl group. In the cyclopropanation with alkenes **13**, the boryl carbene intermediate affords boron-substituted cyclopropane products in high yields with excellent stereoselectivity. A cyclopropene substrate bearing an electron-donating group delivered the cyclopropanation product **16a** in 98% yield and 95% *ee*. Furthermore, substrates containing valuable functional groups such as halogens, cyano (CN), trifluoromethyl (CF_3), and nitro (NO_2) groups also provided the corresponding products (**16b−16e**) with excellent yields and selectivity. Notably, when conjugated dienes were employed as substrates, the initially formed 1,2-divinylcyclopropane products underwent subsequent Cope rearrangement, providing synthetically challenging boron-substituted cycloheptadiene derivatives **17f** and **17g**.

More recently, the Zhu group further leveraged the catalytic system of a copper catalyst and a chiral bis(oxazoline) ligand to achieve highly enantioselective cyclopropanation of alkenes **13** using 1-silylcyclopropene **12** (Scheme 5, **II**).[46] This approach utilizes the copper-catalyzed ring-opening of 1-silylcyclopropene **12** to generate a highly reactive α-silyl-α-vinyl carbenoid, which subsequently participates in cyclopropanation with alkenes **13** to afford polysubstituted asymmetric silylcyclopropane derivatives. This system bypasses the need for unstable and synthetically limited diazo compounds, thereby expanding the structural diversity of silylcyclopropanes.

While the cyclopropanation of alkenes with vinyl carbenes derived from cyclopropene ring-opening is well-established, their application in dearomative cyclopropanation of aromatic systems remains limited. Traditional approaches employing diazo-derived carbenes for indole cyclopropanation face constraints in derivatization versatility and accessibility of polysubstituted allylic diazo precursors.[47] Cyclopropenes offer an alternative route by generating stabilized allylic carbene species. In 2020, Lautens and Jiang independently reported complementary approaches to indole cyclopropanation using

https://doi.org/10.1021/acscatal.5c09031
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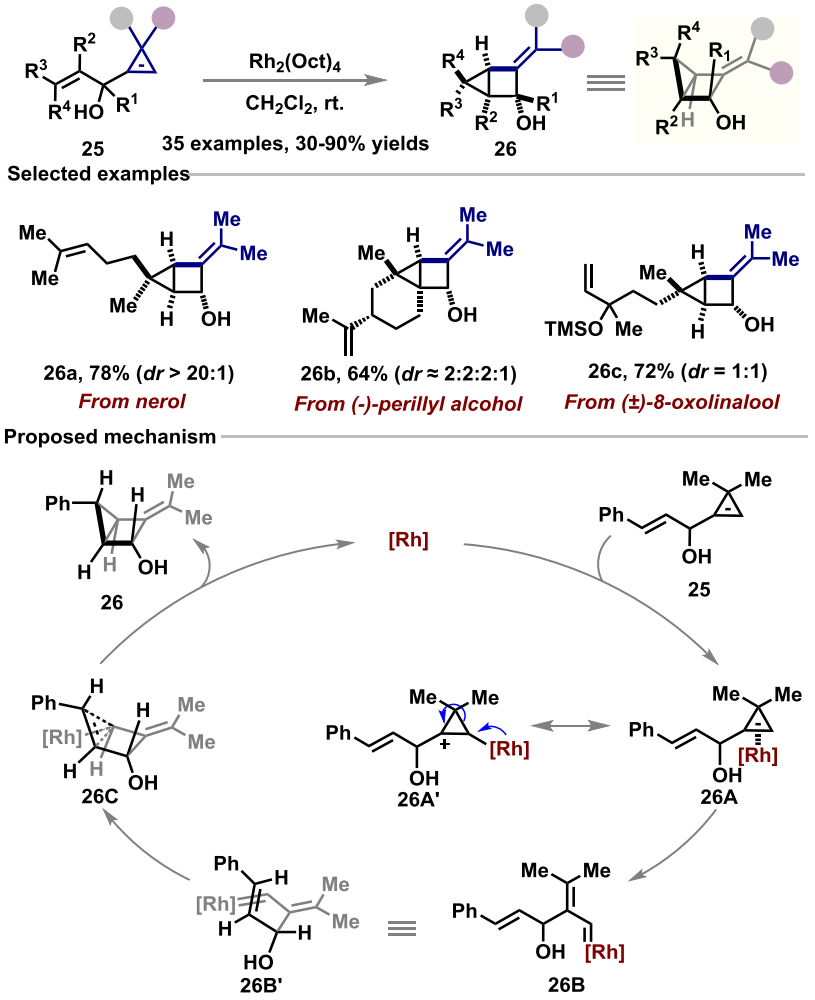
Scheme 8. Synthesis of Housanes from Cyclopropenes *via* Intramolecular Cyclopropanation



cyclopropene precursors. Lautens et al. demonstrated that rhodium(II) acetate dimer ($Rh_2(OAc)_4$)-catalyzed reactions with benzofuran and various indole derivatives proceed under mild conditions with broad substrate scope, yielding cyclopropanation products (**21a−21c**) in high yields, though with moderate stereoselectivity (Scheme 6, **I**).[48] Concurrently, Jiang et al. achieved high stereoselectivity through strategic *N*-sulfonyl protection of indoles, affording vinylcyclopropanes (**22a−22c**) with excellent *E*/*Z* ratios (up to 99:1) and diastereoselectivity (up to >99:1) (Scheme 6, **II**).[49] Mechanistic studies suggest that following rhodium carbene formation **22A** and indole nucleophilic attack, a rhodium 1,3-migration enables bond rotation and cyclization to favor the thermodynamically stable *E*-isomer. Both systems operate efficiently under mild conditions with low catalyst loadings, with Lautens' method offering broader substrate generality and Jiang's approach providing superior stereochemical control.

The inherent aromatic stability of benzene rings renders direct dearomatization particularly challenging.[50] In 2022, Lautens and co-workers demonstrated a rhodium/acid cooperative catalytic system for the dearomative cyclopropanation of 2-naphthols **23** with cyclopropenes **7**, efficiently transforming planar aromatics into three-dimensional architectures (Scheme 7).[51] This system strategically addresses the competing O−H insertion pathway typical of phenol-carbene reactions. Using camphorsulfonic acid (CSA) to promote substrate dehydration, the reaction redirects the transformation toward cyclopropanation, simultaneously suppressing undesired insertion pathways and stabilizing the sensitive dearomatized products. The protocol exhibits broad functional group tolerance (**24a−24e**), though *E*/*Z* selectivity control for the newly formed alkene remains limited. Two mechanistic pathways were proposed: either cyclopropanation of naphthol **23** by vinyl carbene **24A** followed by dehydration (**Path A**), or initial acid-catalyzed dehydration to intermediate **24C** prior to cyclopropanation (**Path B**). While this mild and general method effectively circumvents competing reactions through clever acid cooperation, challenges in stereocontrol and asymmetric induction await further investigation.

In 2024, Vicente and colleagues designed an allyl-substituted cyclopropene as a carbene precursor, which upon Rh(II)-catalyzed ring-opening undergoes stereoselective intramolecular cyclopropanation to construct strained housane frameworks (Scheme 8).[52] This operationally simple and mild catalytic system employs well-define substrate to access diverse housane derivatives through a classic intramolecular cyclopropanation strategy. Notably, the method enables the synthesis of a series of "non-natural" housane-type terpenoids (**26a−26c**), overcoming the limitations of biosynthetic pathways in accessing such architectures. Mechanistic studies

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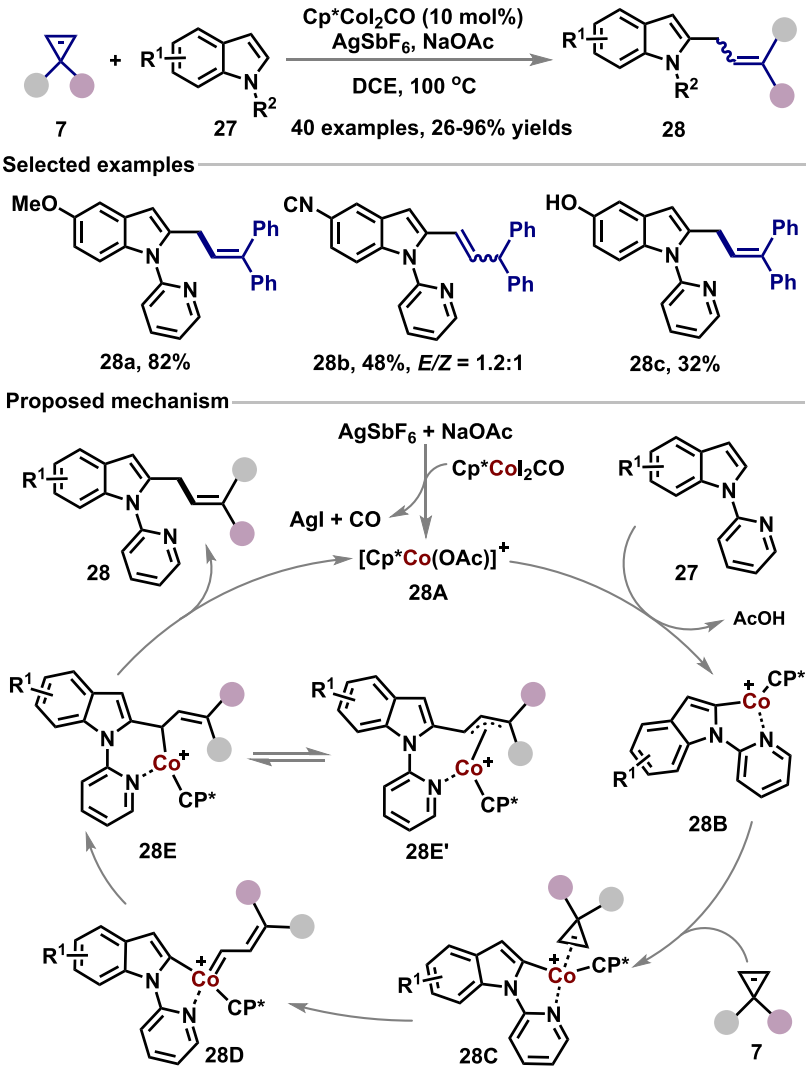
Scheme 9. Co-catalyzed Allylation of Indoles with Cyclopropenes



suggest that rhodium-catalyzed selective ring-opening of cyclopropene **25** proceeds *via* metal-coordination intermediate **26A** to generate vinyl carbene species **26B**. The distorted conformation **26B′**, characterized by significant steric congestion, effectively disfavors nucleophilic attack of the carbene on the hydroxyl group while promoting engagement with the intramolecular alkene. This selective pathway yields intermediate **26C**, ultimately furnishing the housane product **26** bearing exo-oriented hydroxyl and phenyl substituents.

2.2. Insertion Reactions (X−H and C−X) of Vinylcarbenoids

Transition-metal-catalyzed carbene insertion has emerged as a fundamental methodology for constructing C−C and C−X (X = H, B, Si, Se, etc.) bonds, providing distinct advantages in atom and step economy by eliminating requirements for multistep sequences, directing groups, and halogenated reagents. While acceptor and donor/acceptor carbenes have been systematically investigated, the development of donor-type carbenes—particularly vinyl carbenes—has progressed more slowly.[53] Although such transformations were first documented as early as 1913,[54] their advancement has been constrained by a heavy reliance on diazo-based precursors, which present practical limitations due to challenging synthesis, poor stability, and handling difficulties.[55] Recent developments in nondiazo carbene precursors have revitalized this field, enabling novel insertion modalities and expanding synthetic access to vinyl-substituted skeletons.[56] Among these, cyclopropenes have emerged as versatile donor carbene precursors. The strategic design of silyl-, boryl-, and other functionalized cyclopropenes has significantly broadened the insertion landscape,[45,57] facilitating diverse transformations including C−H, B−H, Si−H, Se−H, and C−C bond functionalization.

Carbene C−H insertion represents an atom-economical approach to complex molecular frameworks. When employing cyclopropenes as vinyl carbene precursors, this transformation enables direct installation of allylic functionality. In 2021, Anbarasan and co-workers developed a cobalt-catalyzed system for regioselective C−H insertion at the C2-position of indoles *via* cyclopropene ring-opening process (Scheme 9).[58] Leveraging a pyridyl directing group, the protocol enables indole C−H metalation followed by interception with a vinyl carbene generated from cyclopropene **7**, delivering 2-allylated indole derivatives **28**. The system demonstrates broad functional group tolerance (**28a**−**28c**), though reduced efficiency was observed with cyano-substituted substrates accompanied by conjugate alkene migration **28b**. An allyloxy-

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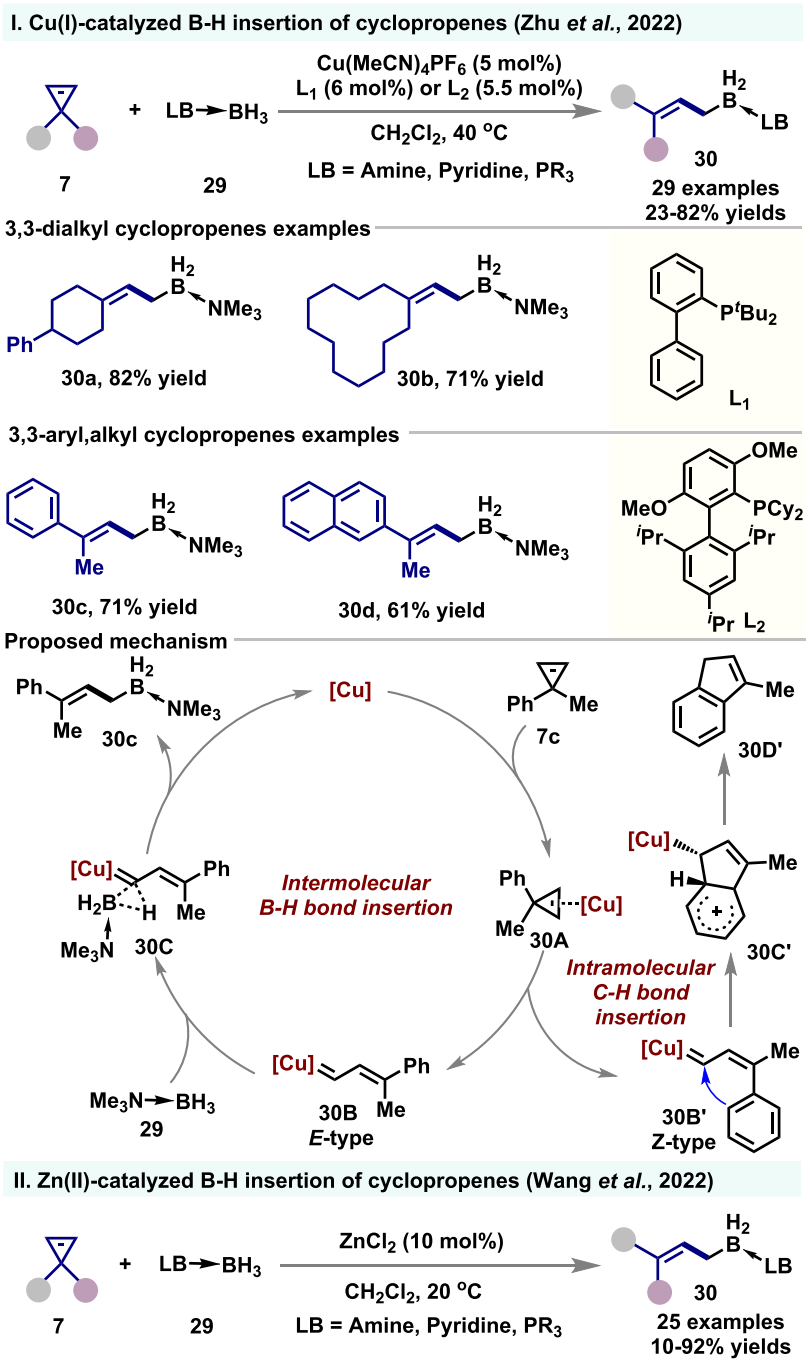
Scheme 10. Transition-Metals Catalyzed B−H Insertion with Cyclopropenes



substituted indole underwent concomitant deprotection to generate the corresponding hydroxy product **28c**. Mechanistic studies suggest ligand exchange generates active cobalt species **28A**, followed by base-assisted C−H metalation to form cyclometalated intermediate **28B** (characterized by HRMS). Subsequent coordination and migratory insertion of cyclopropene **7**, followed by rearrangement, affords cobalt carbene species **28D**. A 1,1-migration then gives intermediate **28E** (or its allylic isomer **28E′**), with final demetalation affording the corresponding product **28**. This work represents a unqiue example of cobalt-catalyzed cyclopropene ring-opening to vinyl cobalt carbenes. However, controlling *E*/*Z* selectivity in unsymmetrical cyclopropene substrates remains a significant challenge.

Since the pioneer work by Curran and co-workers in 2013 on transition-metal-catalyzed carbene B−H bond insertion,[59] this strategy has evolved into a powerful methodology for C−B bond construction. Conventional carbene precursors such as diazo compounds, alkynes, and sulfur ylides have been successfully employed to access diverse organoboron compounds.[60] However, cyclopropenes remained unexplored for B−H insertion for nearly a decade. In 2022, the Zhu group addressed this issue by reporting a copper-catalyzed B−H insertion *via* cyclopropene ring-opening, enabling efficient C−B bond formation and yielding stable allylborane-Lewis base adducts **30** (Scheme 10, **I**).[61] Control experiments revealed that only trace product was detected in the absence of ligand, with cyclopropene dimerization

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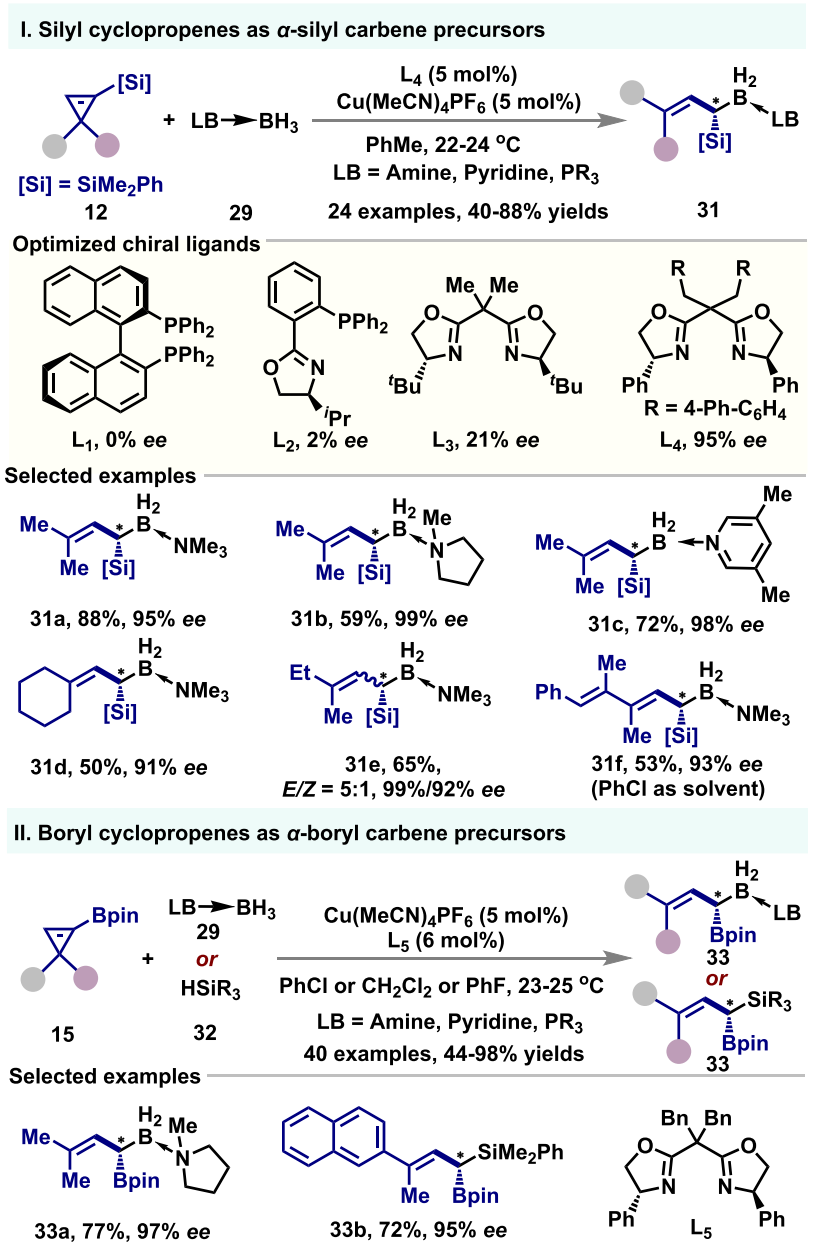
Scheme 11. Enantioselective B−H and Si−H Insertion with Cyclopropenes



dominating as the major pathway. While bidentate phosphine ligands failed to improve yield, the monodentate JohnPhos (L_1) significantly enhanced the formation of **30a**. The system exhibited broad applicability toward symmetric 3,3-dialkyl substituted cyclopropenes **30b**, while sterically demanding ligands enabled stereocontrol in unsymmetrical variants (**30c**−**30d**). Mechanistic studies indicated that copper catalysis promotes selective ring-opening to form *E*-configured carbene **30B** or *Z*-configured carbene **30B′**. The *E*-isomer is trapped by the borane adduct, forming intermediate **30C** that evolves *via* demetalation to give the intermolecular B−H insertion product **30c**, whereas the *Z*-isomer preferentially undergoes intramolecular C−H insertion to generate byproduct **30D′**. Concurrently, the Wang group developed a zinc salt-catalyzed B−H insertion between cyclopropene **7** and borane adducts, providing efficient access to allylboron products **30** with high stereoselectivity without requiring exogenous ligands (Scheme 10, **II**).[62] In contrast to the Zhu group's ligand-dependent system, the zinc-based catalysis achieves excellent stereocontrol under ligand-free conditions. These complementary approaches significantly expand the synthetic utility of cyclopropenes in B−H insertion chemistry.

While insertion chemistry of α-alkyl carbenes has been extensively developed, the asymmetric insertion of α-silyl carbenes remains largely unexplored, primarily constrained by two fundamental challenges: the limited availability of efficient α-silyl carbene precursors and the difficulty in designing catalytic systems capable of achieving high enantioselectivity. Building upon their pioneering work on cyclopropene-derived α-vinyl carbenes in B−H insertion reactions,[61] the Zhu group achieved a breakthrough in 2022 by employing 1-silylcyclopropene **12** as an α-silyl carbene precursor for enantioselective B−H insertion with borane adduct **29** (Scheme 11, **I**).[56] This methodology provides direct access to chiral γ,γ-disubstituted allylic *gem*-

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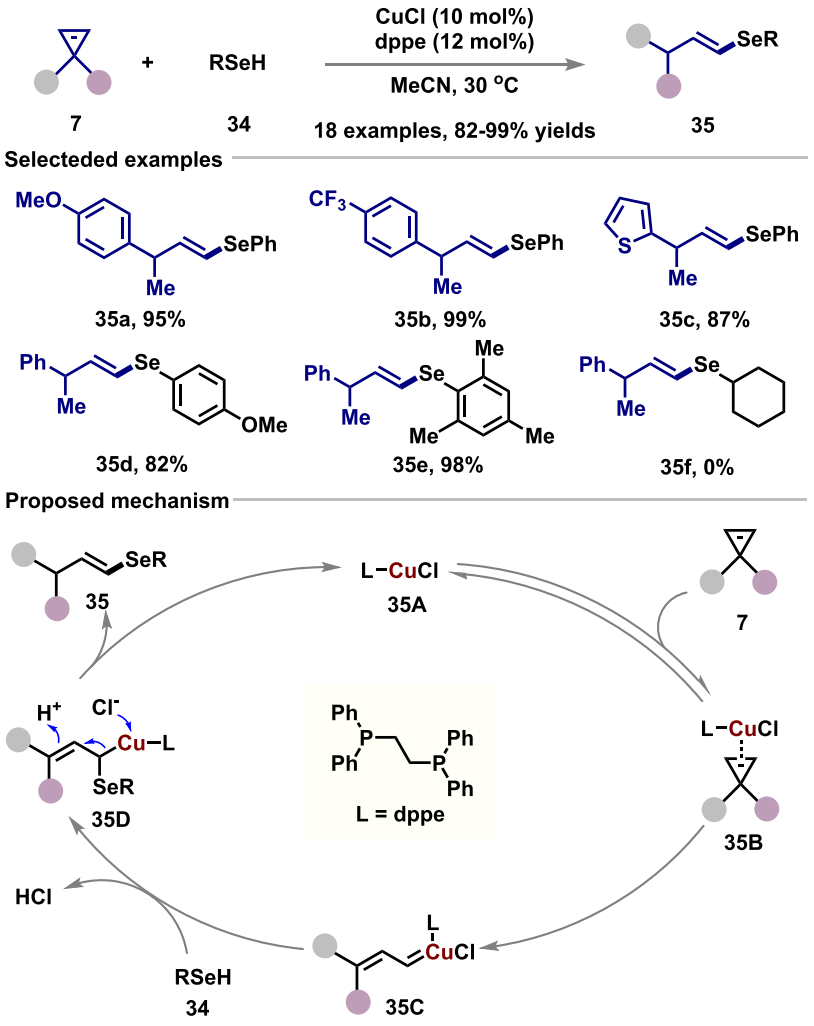
Scheme 12. Cu-Catalyzed Se−H Insertion with Cyclopropenes



silicon−boron compounds. Systematic ligand optimization identified a catalytic system comprising tetrakis(acetonitrile)-copper(I) hexafluorophosphate ($Cu(MeCN)_4PF_6$) and bis-(oxazoline) ligand L_4 as optimal for enantiocontrol, delivering product **31a** with up to 95% *ee*. The protocol demonstrated broad substrate scope, accommodating both cyclic amine- and pyridine-derived borane adducts (**31b**−**31c**) while showing excellent compatibility with diverse cyclopropene substitution patterns. Although modest stereoselectivity was observed with sterically undemanding acyclic alkyl-substituted unsymmetrical cyclopropenes **31e**, substrates featuring 3-alkenyl substituents afforded product **31f** with excellent enantioselectivity. This work establishes the first general platform for enantioselective α-silyl carbene transfer, significantly expanding the synthetic utility of silylcarbene chemistry in complex chiral molecule assembly.

In 2024, the Zhu group further advanced a Cu-$(MeCN)_4PF_6$/bis(oxazoline) L_5 catalytic system that enables highly enantioselective B−H and Si−H insertions with 1-borylcyclopropene **15**, facilitating the construction of valuable vinyl gem-diboron and gem-silicon−boron skeletons (Scheme 11, **II**).[45] Various borane adducts underwent efficient transformation with 3,3-dialkyl-1-borylcyclopropenes, with tertiary amine-boranes delivering products such as **33a** with excellent efficiency and stereoselectivity. Both electronic and steric modifications on aryl substituents minimally affected reaction performance, and a naphthyl-substituted cyclopropene provided **33b** in 72% yield with 95% *ee*. Mechanistic investigations revealed cyclopropene ring-opening as the rate-determining step, with the Bpin group crucially modulating both stereochemical outcome and electronic properties. These complementary catalytic systems, operating under mild conditions with earth-abundant copper catalysts, enable efficient assembly of high-value organoboron and organosilicon frameworks, demonstrating considerable potential for industrial implementation.

While transition metal-catalyzed carbene insertions into C−H, B−H, and Si−H bonds have been extensively documented, analogous transformations involving Se−H bonds remain notably underdeveloped.[63] Recently, the Yang group addressed this gap through a copper(I)-catalyzed Se−H insertion employing cyclopropene ring-opening followed by isomerization to access vinyl selenoether derivatives (Scheme 12).[64] The protocol demonstrates excellent generality across aryl-substituted cyclopropenes and substituted aryl selenols, delivering products (**35a**−**35e**) with high efficiency. Notably, aliphatic selenols proved unreactive under the optimized conditions **35f**. Mechanistic studies support a classical carbene transfer pathway initiated by π-coordination of Cu(I) to the cyclopropene double bond, forming activated complex **35B** with significantly attenuated C−C bond strength. Driven by substantial ring strain, regioselective C−

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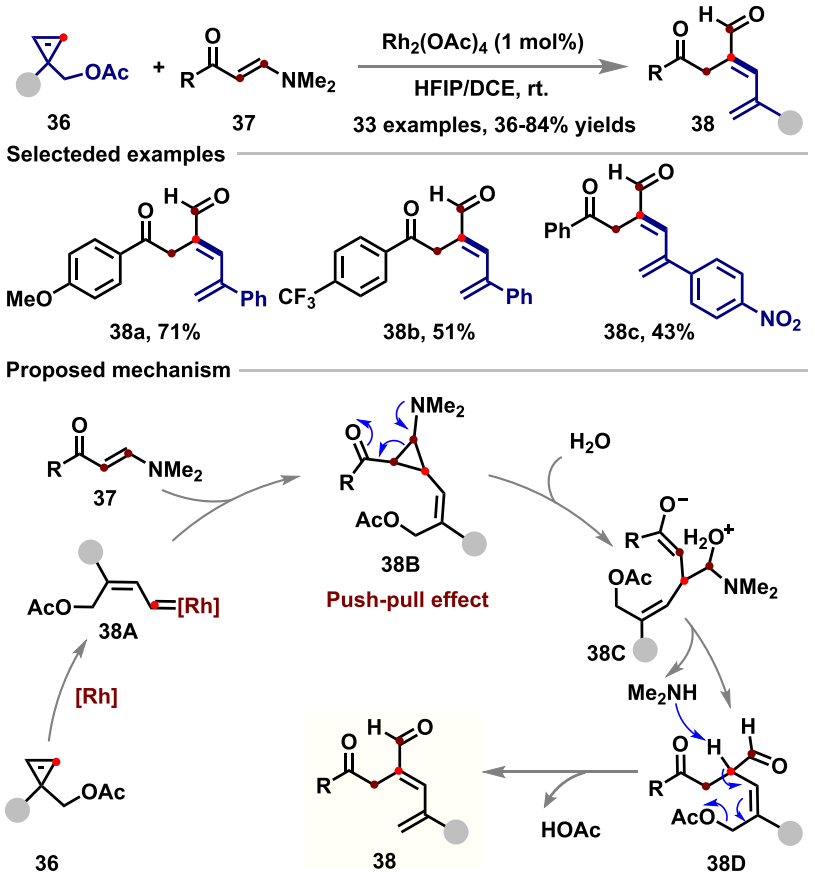
Scheme 13. Rh-Catalyzed Csp^2 Insertion into C═C Bonds with Cyclopropenes



C bond cleavage generates the key vinyl copper-carbenoid **35C**, identified as the rate-determining step. Subsequent nucleophilic attack by the selenol at the electrophilic carbene center forms Cu−Se bonded species **35D**, which undergoes protonolysis to release the vinyl selenoether product **35** while regenerating the active copper catalyst.

Single-carbon skeletal editing has garnered significant attention in recent years as a powerful strategy for molecular diversification and scaffold hopping in drug discovery.[65] While remarkable progress has been achieved in single-carbon insertion into cyclic frameworks, selective cleavage and precise carbon insertion into acyclic systems—particularly unsaturated carbon chains—have remained comparatively underdeveloped.[66] Notably, the Jiang group has comprehensive investigated the cleavage and single-carbon insertion of unsaturated C−C bonds using carbene precursors as C_1 synthons since 2017.[67] In 2019, they employed cyclopropene derivatives as C_1 units to achieve formal cleavage and carbon insertion into the unsaturated C−C bonds of enaminones, leading to vinyl aldehydes.[68] In 2021, the team further reported a rhodium-catalyzed formal single-carbon C(sp^2) insertion using well-defined cyclopropene **36** bearing a leaving group (Scheme 13).[69] Strain-driven ring-opening generates a vinyl carbene intermediate that reacts with enaminone **37** to efficiently construct structurally diverse and highly functionalized 1,3-dienes **38**. The transformation demonstrates broad substrate scope, accommodating variously substituted enaminones and cyclopropenes (**38a**−**38c**). Control experiments confirmed selective cleavage of the enaminone C═C bond concomitant with cyclopropene ring-opening and insertion, enabling new C═C bond formation. The proposed mechanism involves several key steps: rhodium-catalyzed cyclopropene ring-opening to vinyl carbene **38A**; cyclopropanation forming aminocyclopropane **38B**; push−pull facilitated cyclopropane cleavage; and hydrolysis/rearrangement to final dienone **38**. This elegant sequence demonstrates the power of carbene-mediated single-carbon insertion for complex molecular transformations.

Despite established methodologies for generating vinyl carbenes through cyclopropene ring-opening, stereocontrol of the resulting C═C bond—particularly *E*/*Z* stereoselectivity—remains a significant challenge. In 2023, the Jiang group addressed this problem using hydroxy-substituted enaminones under zinc catalysis, achieving divergent syntheses of 1,3- and 1,4-dicarbonyl compounds with exceptional stereoselectivity (Scheme 14).[70] The proposed mechanism involves zinc-promoted ring-opening of cyclopropene to form vinyl zinc carbene complex **40A**. In Path A, BF_3-complexed enaminone **39** undergoes cyclopropanation to form **40B**, which undergoes selective bond cleavage and iminium hydrolysis to yield 1,3-dicarbonyl product **40**. Alternatively, Path B proceeds through cyclopropane intermediate **40D**, where selective cleavage of the original enaminone C═C bond ultimately affords formal single-carbon insertion product **41**. Notably, both experimental and DFT calculation studies revealed the critical role of the hydroxyl group in controlling *E*/*Z* stereoselectivity. In this reaction, *E*/*Z* stereoselectivity is mainly controlled by coordination of the hydroxyl group with either BF_3 or $ZnBr_2$. This interaction introduces steric effect

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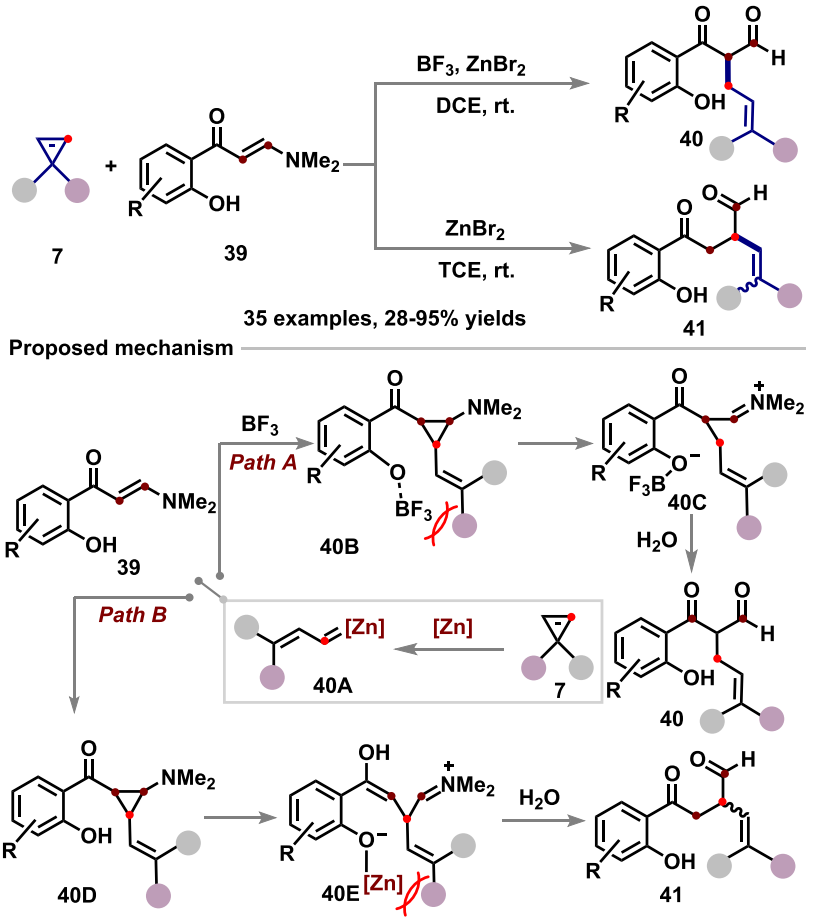
Scheme 14. Chemo- and Setero-Selective C−H Insertion and C═C Insertion with Cyclopropenes



that favors the *E*-configured intermediates **40B** and **40E**, leading predominantly to *E*-products.

Compared to C═C double bonds, the higher bond dissociation energy of C≡C triple bonds renders formal single-carbon insertion substantially more challenging. In 2022, the Jiang group addressed these challenges by developing a cooperative amine/rhodium dual catalytic system that enables efficient single-carbon insertion into conjugated alkynes under mild conditions, providing diverse α-vinyl-1,4-dicarbonyl compounds (Scheme 15).[71] This catalytic system operates under mild conditions with broad substrate scope. The incorporation of chiral amine and chiral rhodium catalysts enabled preliminary exploration of an asymmetric C≡C bond cleavage/insertion platform. However, the enantioselectivity was compromised by subsequent enolization of the α-vinyl carbonyl products, though chiral induction was observed in the initial transformation (**43a**−**43c**). The proposed mechanism involves amine-catalyzed conversion of the alkyne to enaminone intermediate **43B**, effectively cleaving one π-bond of the C≡C triple bond. Concurrently, rhodium-catalyzed cyclopropene ring-opening generates reactive metal-carbene species **43A**.

Cyclopropanation between **43B** and **43A** forms key aminocyclopropane intermediate **43C**, which undergoes C−C σ-bond cleavage facilitated by synergistic electronic effects between the carbonyl and amino groups, completing the formal triple bond cleavage. Hydrolysis and amine elimination then afford the single-carbon insertion product **43** while regenerating the amine catalyst. Notably, recent DFT calculations by the Li group provided additional mechanistic validation, offering detailed insights into this transformation.[72]

The Büchner reaction, first documented in 1885, constitutes a cornerstone transformation in organic synthesis through its unique carbene insertion/electrocyclic rearrangement mechanism to access seven-membered carbocycles.[73] While modern transition-metal catalysis has enhanced selectivity in this transformation, intermolecular asymmetric versions remain fundamentally challenging.[74] In 2024, Jiang and co-workers reported a rhodium−boron cooperative catalytic system that enables asymmetric Büchner-type reactions *via* phenolic cyclopropanation and ring expansion (Scheme 16).[75] This strategy employs a Lewis acidic boron reagent to transiently protect the phenolic hydroxyl, simultaneously suppressing competitive O−H insertion and promoting subsequent ring expansion. The system delivers multifunctionalized cycloheptadienones **45** with excellent regio- and enantioselectivity across diverse substrates (**45a**−**45c**). DFT calculations and isotopic labeling experiments confirm the boron reagent's dual role: interacting with the phenolic hydroxyl and facilitating keto−enol tautomerization. The proposed mechanism involves rhodium-catalyzed cyclopropene ring-opening to vinyl carbene **45A**, cyclopropanation to form **45B**, boron-assisted tautomerization to **45C**, and selective ring expansion to the final cycloheptadienone **45**. This methodology establishes a new paradigm for asymmetric single-carbon insertion of aromatic systems.

Classical Büchner reactions typically rely on transition metals such as Rh, Pd, or Cu to generate metal-carbene

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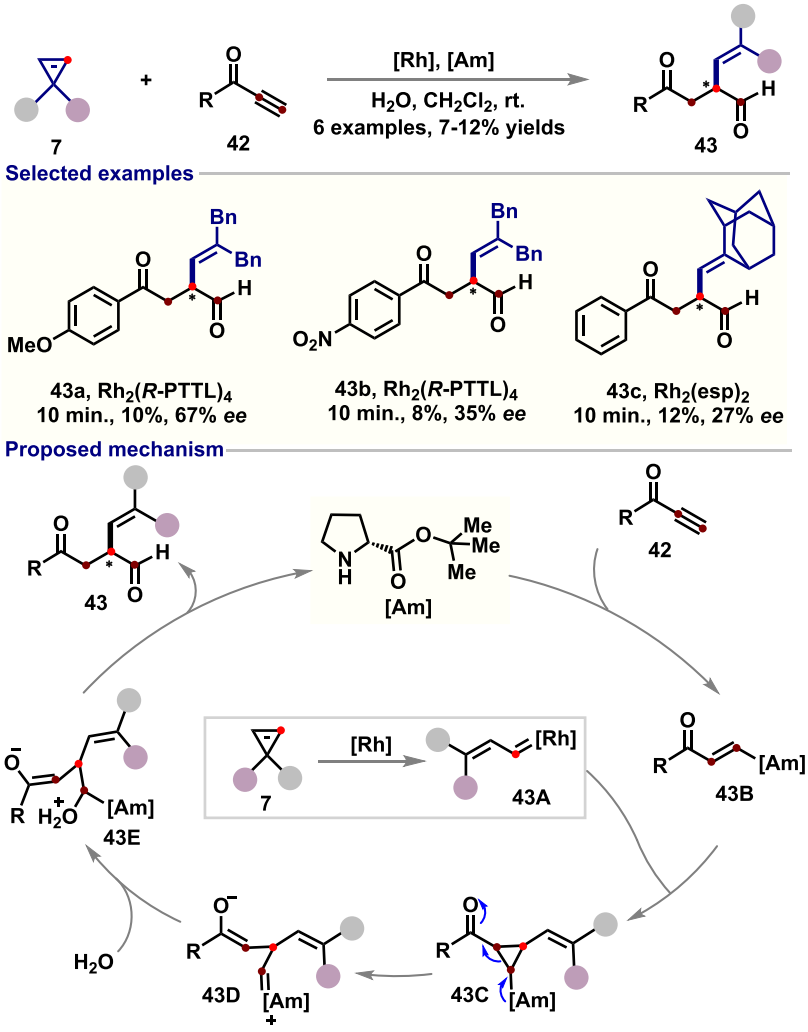
Scheme 15. Rh-Catalyzed C≡C Bonds Insertion with Cyclopropenes



complexes for arene ring expansion. Recently, the Wang group demonstrated a paradigm shift by reporting the first chalcogen-bonding catalyzed Büchner reaction (Scheme 17).[76] This work establishes an organocatalytic platform for cyclopropene ring-opening and aromatic ring expansion, offering a novel strategy for carbene transformations. Conventional metal catalysis or thermal conditions predominantly afford furan byproducts **47** *via* nucleophilic attack of the carbonyl oxygen on the carbene intermediate, with only trace ring-expansion products detected. In contrast, introduction of a phosphono-chalcogenide chalcogen (PCH)-bond donor redirects the pathway toward selective arene cyclization, efficiently affording ring-expanded product **48**. A proposed mechanism involves chalcogen-bonding activation of the cyclopropene through *Se-π* interaction **48A** or synergistic *Se-π*/*Se*−*O* coordination **48A′**. This activation enables ring-opening to generate carbene species **48B** (in resonance with carbocation **48B″**). Critical *Se*−*O* interaction suppresses carbonyl attack, diverting the carbene toward arene cyclization to form **48C**, which subsequently undergoes intramolecular cyclization to complete the ring expansion.

In contrast to conventional single-carbon insertion reactions into unsaturated carbocycles *via* cyclopropanation process, the skeletal expansion of saturated *N*-heterocycles presents more synthetic challenges. Recently, the Peng group disclosed a copper-catalytic system that enables formal single-carbon insertion into C−N bond of imidazolidines, employing vinyl copper carbene intermediates generated from cyclopropene ring-opening to construct 2-vinylpiperazine architectures (Scheme 18).[77] This method exhibits excellent substrate compatibility and regioselectivity. Cyclopropene derivatives bearing either electron-donating **50a** or electron-withdrawing groups **50b**, as well as a sterically demanding adamantyl substituent **50d**, all afforded the corresponding 2-vinylpiperazine products in good yields. Regarding the imidazolidine scope, *N*-benzyl-substituted substrates demonstrated good compatibility with variously substituted aromatic rings **50e**. Remarkably, complete regioselectivity and exclusive *E*-configurational selectivity were maintained even with unsymmetrically substituted imidazolidine substrates **50f**. Mechanistic investigations support a concerted ring-opening/ring-closing pathway. Initial copper-catalyzed cyclopropene ring opening generates the key vinyl copper carbene intermediate **50A**, which undergoes nucleophilic attack by the imidazolidine nitrogen to form zwitterionic specie **50B**. Subsequent C−N bond cleavage affords an acyclic iminium ion intermediate **50C**, followed by intramolecular amino-cyclization to deliver the 2-vinylpiperazine product **50**, representing formal single-carbon insertion into the C−N bond. This methodology not only achieves scaffold hopping

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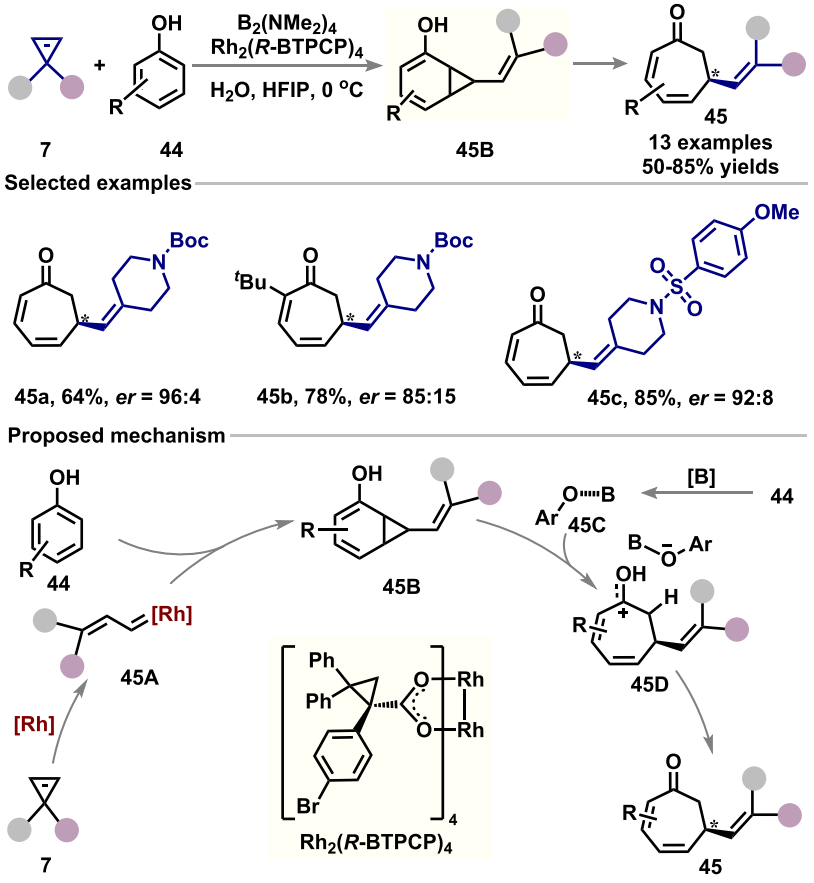
Scheme 16. Asymmetric Büchner Reaction of Phenols with Cyclopropenes



from five-membered to six-membered *N*-heterocycles but also expands the utility of cyclopropenes as single-carbon synthons in framework modification.

2.3. Cyclizations of Cyclopropenes as Vinylcarbeniods

Cyclization reactions represent fundamental strategies for constructing carbocyclic and heterocyclic frameworks.[78] While carbenes have been widely employed as reactive intermediates in ring formation, traditional precursors such as diazo compounds face limitations including instability, toxicity, and functional group intolerance.[79] Although hydrazone derivatives offer improved safety profiles, their low atom economy and harsh reaction conditions restrict applications in complex molecule synthesis.[80] Cyclopropenes, as the smallest unsaturated carbocycles, possess unique reactivity derived from ring strain and an endocyclic double bond, serving as versatile C_1, C_2, or C_3 synthons in various cyclization modes.[81] Recent advances in transition-metal-catalyzed ring-opening have enabled their application in [3 + 1], [4 + 1], [2 + 2 + 1], and [3 + 2] cycloadditions, facilitating access to four- to six-membered and larger ring systems. These developments establish cyclopropenes as complementary precursors to traditional carbene sources for diverse cyclic architectures.

The incorporation of fluorine into heterocycles significantly modulates pharmaceutical properties including lipophilicity, metabolic stability, and membrane permeability.[82] Despite this importance, methods for constructing fluorinated azetidines *via* [3 + 1] cyclization remain underdeveloped. In 2021, the Zhang group addressed this gap through a copper-catalyzed [3 + 1] annulation between cyclopropene **7** and α-bromodifluoroacetamides **51**, providing direct access to structurally diverse α,α-difluoro-β-lactam derivatives **52** (Scheme 19).[83] The transformation demonstrates broad substrate scope, accommodating various *N*-aryl-α-bromodiuoroacetamides (**52a**−**52b**) and cyclopropenes bearing isopropyl or thienyl substituents (**52c**−**52d**). However, poor *E*/*Z* selectivity (1:1) was observed with unsymmetrical isopropyl-substituted cyclopropenes **52c**. The proposed mechanism involves copper-catalyzed ring-opening to vinyl copper-carbenoid **52B**, which undergoes nucleophilic attack by deprotonated acetamide **52C**, followed by intramolecular cyclization to form the β-lactam products **52**. This mild and efficient catalytic system provides valuable access to fluorinated azetidines, though challenges in stereocontrol remain to be addressed.

Cyclopropenes have emerged as versatile building blocks extending beyond strained four-membered ring synthesis to enable efficient construction of five-membered carbocyclic architectures. In 2024, the Tsurugi group reported a niobium-catalyzed intermolecular [2 + 2 + 1] cycloaddition employing cyclopropene **7** as a C_1 synthon with two alkynes **53**, delivering polysubstituted cyclopentadiene derivatives (Scheme 20, **I**).[84] Mechanistic studies reveal that niobium(V) chloride ($NbCl_5$) undergoes single-electron reduction to form a Nb(IV) species, which coordinates with triphenylphosphine (PPh_3) to generate dinuclear complex **54A**. Subsequent reduction and alkyne **53** coordination generates η^2-alkyne Nb(III) complex **54B**. Cyclopropene **7** then undergoes 1,2-insertion to form metallacyclopentene **54C**, which undergoes β-carbon elimination *via* cyclopropane opening to afford

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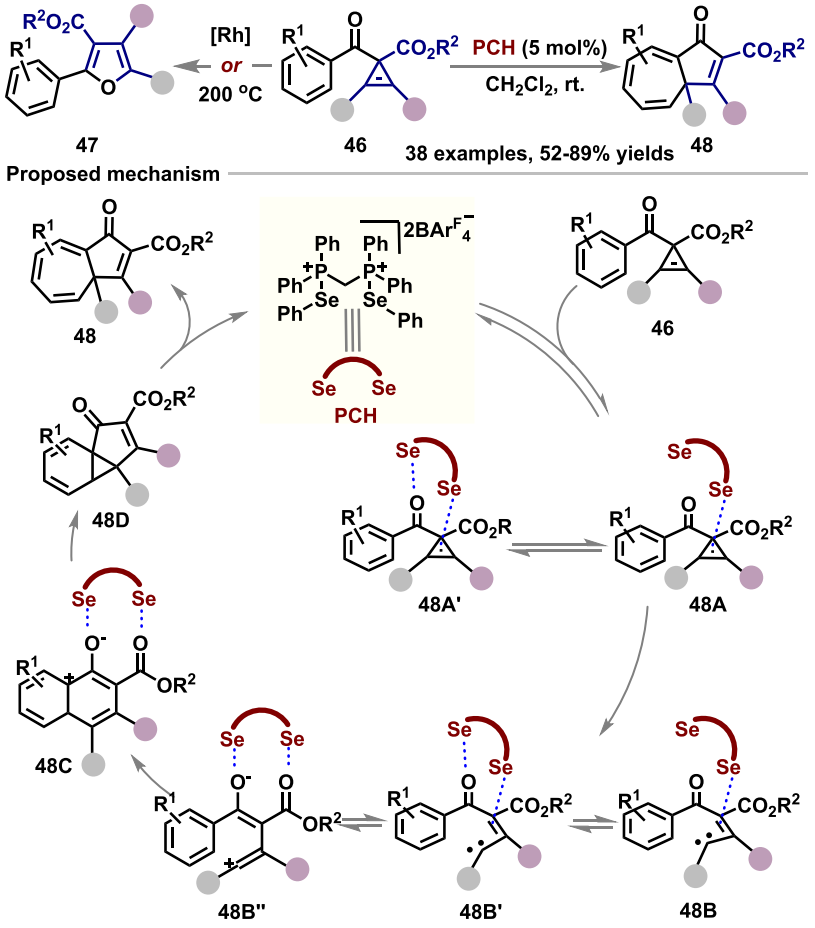
Scheme 17. Chalcogen Bonding Catalysis Enables Ring-Opening of Cyclopropenes



dienyl carbene **54D**. Carbene/alkyne metathesis with a second alkyne **53** generates trienyl carbene **54E**, which undergoes 6π-electrocyclization to metallacyclohexadiene **54F**. Reductive elimination forms niobium-coordinated cyclopentadiene **54G**, and ligand exchange with another alkyne releases the product while regenerating active species **54H**. The PPh_3 ligand crucially suppresses niobium(III) chloride ($NbCl_3$) polymerization and stabilizes the active niobium centers. Recently, Tsurugi extended this strategy to a tungsten-based system, developing a W(IV)-catalyzed [2 + 2 + 1] cycloaddition between cyclopropene **7** and alkyne **53** (Scheme 20, **II**).[85] This system affords polysubstituted cyclopentadienes with >99% *E*-selectivity, significantly outperforming the niobium counterpart. Mechanistic studies confirm a vinyl carbene-initiated pathway involving C−C bond cleavage, sequential alkyne metathesis, and 6π-electrocyclization to complete the catalytic cycle. This mild catalytic system exhibits broad substrate scope and excellent functional group tolerance. The mechanistic framework provides fundamental insights for designing low-valent niobium catalysts, overcoming traditional [2 + 2 + 1] cycloadditions' reliance on CO or highly reactive metal reagents.

While C−C σ-bond cleavage of cyclopropenes has been extensively exploited for metal-carbene generation, selective activation and cleavage of their C=C double bonds remained largely unexplored. In 2023, the Yamamoto group addressed this challenge by designing remotely alkyne-tethered cyclopropene derivatives that undergo ruthenium-catalyzed intramolecular cycloaddition *via* selective C=C bond cleavage, efficiently producing 1,2-fused cyclopentadienes and polysubstituted cycloheptatrienes **58** (Scheme 21).[86] DFT calculations reveal a mechanism initiated by coordination of the cyclopropene-alkyne substrate **57** to the ruthenium center, followed by oxidative cyclization to form a fused ruthenacyclopentene intermediate **58A**. Isomerization to a six-membered dicarbene species **58B** and subsequent reductive elimination affords the cyclopentadiene product **58**. The system tolerates various C3-substituted cyclopropenes (**58a**−**58b**), though substrates with substituents at the alkyne terminus favor furan byproduct formation. Notably, removal of the ester group from the cyclopropene ring enabled formation of product **58c** in 89% yield at elevated temperature. Extension to cyclopropene-diyne systems achieved sequential alkyne insertion, efficiently delivering polysubstituted heptatrienes (**58d**−**58f**). Conducted under dilute conditions with chloro(1,5-cyclooctadiene)(η^5-pentamethylcyclopentadienyl)ruthenium (Cp*RuCl(cod)) catalyst, this approach effectively suppresses competing pathways despite requiring elevated catalyst loadings.

In 2024, the López group disclosed a related intramolecular (3 + 2) annulation using alkynyl-tethered cyclopropenes **59** as C_3 synthons under cobalt catalysis (Scheme 22).[87] This system efficiently constructs polysubstituted 1,2-fused cyclopentadienes **60** under mild conditions. Diverging from Yamamoto's C=C cleavage pathway, the cobalt-catalyzed mechanism proceeds through selective C−C σ-bond cleavage of the cyclopropene to generate a key metal-carbene intermediate. The cobalt catalytic system exhibits exceptional

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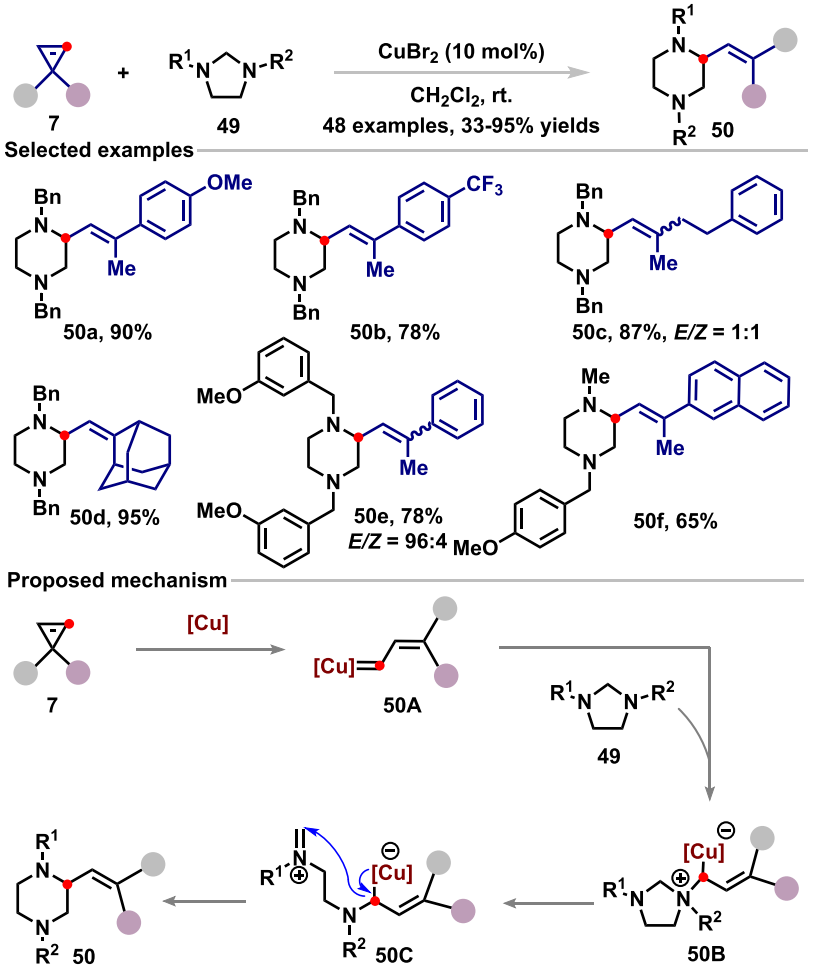
ACS Catal. 2026, 16, 3013−3071

Scheme 18. Cu-Catalyzed C−N Insertion with Cyclopropenes



substrate scope and functional group tolerance: alkyne-tethered cyclopropenes bearing electron-withdrawing malonate substituents undergo quantitative conversion to **60a**; sterically hindered silyl-substituted **60b** and amide-containing substrates **60c** also efficiently form the bicyclic products. Mechanistic studies suggest a singlet−triplet interconversion pathway. $CoBr_2$ is reduced by indium to a low-valent Co(I) species, which coordinates with the dppp ligand to form the active complex **60A**. Coordination of alkyne **59** to the triplet Co(I) species forms intermediate **60B**, followed by C−C σ-bond cleavage to generate singlet cobalt-carbene **60C**. Intramolecular [2 + 2] cycloaddition forms cobalt−cyclobutene complex **60D**, which rearranges to lower-energy triplet species **60E**. Final reductive elimination and hydride migration afford product **60**. Carbonyl−cobalt coordination is proposed to alleviate steric congestion at the catalytic site, facilitating the triplet-state reductive elimination. This earth-abundant cobalt platform overcomes the reliance on precious Rh/Ru catalysts in conventional cyclopropene activation. While an asymmetric version remains undeveloped, incorporation of chiral ligands could enable potential enantioselective transformations for pharmaceutical applications.

Recent advances in transition-metal-catalyzed C−H functionalization have established carbene transfer as a powerful strategy for heterocycle synthesis.[88] While traditional approaches rely heavily on diazo compounds as C_1 synthons, cyclopropenes have emerged as versatile alternatives whose reactivity can be strategically modulated to function as C_1, C_2, or C_3 synthons through catalyst design. The synthetic potential of cyclopropenes in C−H annulation was initially demonstrated by the Wang group (2014), where pentamethylcyclopentadienyl rhodium dichloride dimer ($[Cp^*RhCl_2]_2$)-catalyzed reaction with *N*-phenoxyacetamides **61** employed cyclopropenes as C_3 synthons to access *2H*-chromenes **62** (Scheme 23, **I**).[89] In contrast, the Rovis group showcased their utility as C_2 synthons in formal [4 + 2] annulations with aryl amides **63** to construct isoquinolinone derivatives **64**, using CsOAc as the base to promote C−H deprotonation and construct isoquinolinone derivatives **64**. (Scheme 23, **II**).[90] Notably, the Cao group achieved a remarkable switch in cyclopropene reactivity through precise control of the $[Cp^*RhCl_2]_2$ catalytic system by replacing the base with AgOAc, developing a [4 + 1] annulation where cyclopropene serves as a C_1 synthon (Scheme 23, **III**).[91] Crucially, replacing CsOAc with AgOAc leads to a change in the reaction mechanism. AgOAc not only activates the catalyst through ligand exchange, but the weak coordination of Ag^+ also plays a key role in control the reaction selectivity. Meanwhile, Ag^+ serves as the oxidant to oxidize Rh(I). This transformation between *N*-alkoxybenzamides **65** and cyclopropene **7** affords isobenzofuranone *O*-alkyl oxime products through a C−H activation pathway. Mechanistic studies reveal that the active Cp*Rh(III) species **66A** undergoes C−H metalation to form cyclometalated intermediate **66B**.

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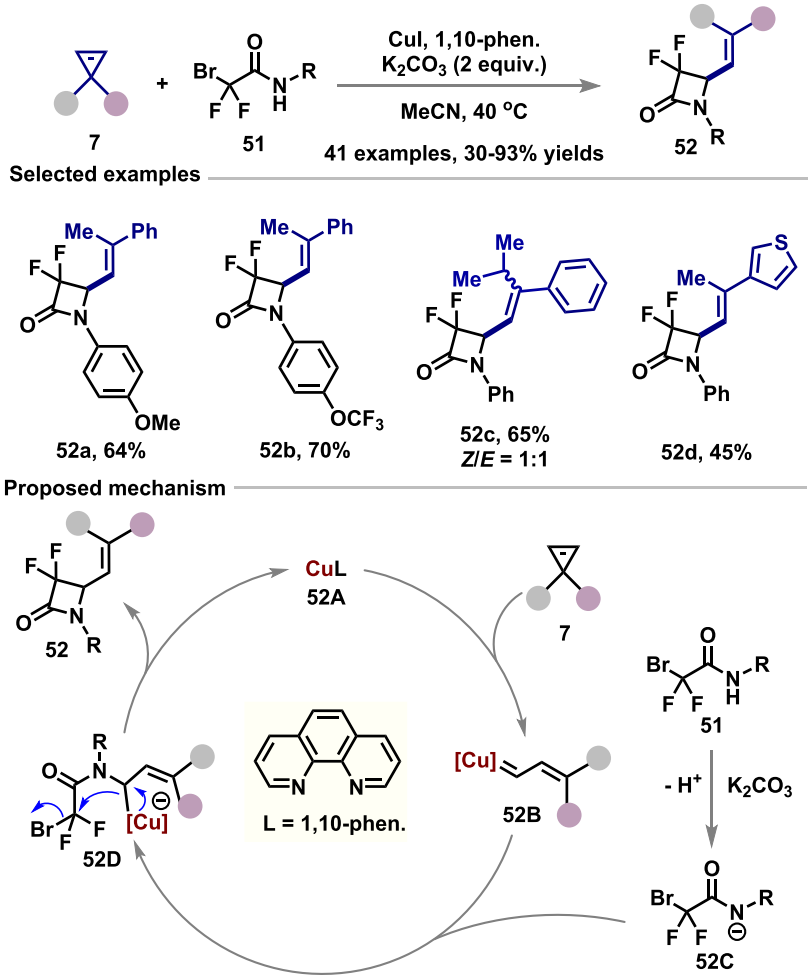
Scheme 19. Cu-Catalyzed [3 + 1] Cyclization of α-Bromo, α,α-Difluoroamides with Cyclopropenes



Subsequent 1,1-insertion of cyclopropene generates rhodium carbene **66C**, which rearranges to allyl-rhodium species **66D**. Competition between *O*- and *N*-attack pathways from **66D′** is resolved in favor of *O*-attack due to severe steric repulsion between the alkoxy group and Cp* ligand in the *N*-attack transition state. The sterically unencumbered *O*-attack pathway leads to C−O bond formation *via* **66E**, with reductive elimination delivering product **66** while regenerating the catalyst through silver acetate (AgOAc)-mediated oxidation. This work significantly expands the synthetic versatility of cyclopropenes in transition-metal-catalyzed C−H functionalization and annulation chemistry.

Based on previous C−H functionalization achievements, Anbarasan and co-workers have recently achieved a significant advance in asymmetric annulation of cyclopropenes by employing rational designed chiral rhodium catalysts (Scheme 24, **I**).[92] A chiral cyclopentadienyl-ligated Rh(III) complex enables an asymmetric [4 + 1] annulation between cyclopropenes as C_1 synthons and *N*-(*tert*-butoxy)-benzamides, providing efficient access to chiral five-membered *aza*-heterocycles. This catalytic system demonstrates good substrate generality for the synthesis of asymmetric vinyl substituted isoindolinones. For the aryl hydroxamate derivatives, the *ortho*-methyl-substituted substrate **67a** gave a low yield may due to steric hindrance, yet still with excellent enantioselectivity. The electron-withdrawing trifluoromethyl-substituted substrate **67b** was obtained in 97% yield with 86% *ee*. Regarding the cyclopropenes, the 3-fluoro-3-phenylcyclopropene afforded the product **67c** with high enantioselectivity, while the different substituted cyclopropene **67d** generated a mixture of *E*/*Z* isomers. A key finding reveals that steric parameters of the [Rh]-I ligand dictate reaction outcomes: substituents at the 3,3′-positions govern chemoselectivity, while Cp-ring substitution patterns control facial selectivity to determine enantioconfiguration. This sophisticated steric modulation enables selective formation of [4 + 1]-type isoindolinones, distinguishing itself from Cao's *O*- attack pathway through direct *N*-attack cyclization. The proposed mechanism involves Cp*Rh(III)-catalyzed C−H metalation to form cyclometalated intermediate **67B**, followed by insertion of cyclopropene to generate rhodium carbene **67C**. Subsequent C−N bond formation constructs the isoindolinone framework **67**, with catalyst regeneration completing the catalytic cycle. Extending this strategy, the same group developed an asymmetric [4 + 1] annulation between aromatic carboxylic acids **68** and cyclopropene **7** using analogous chiral [Rh]-II catalysis (Scheme 24, **II**).[93] This mild protocol delivers chiral 3-alkenyl phthalides **69** with excellent functional group tolerance and stereocontrol. Notably, the methodology demonstrates remarkable utility in late-stage functionalization of drug-like molecules **69a**, highlighting its potential in complex molecule synthesis.

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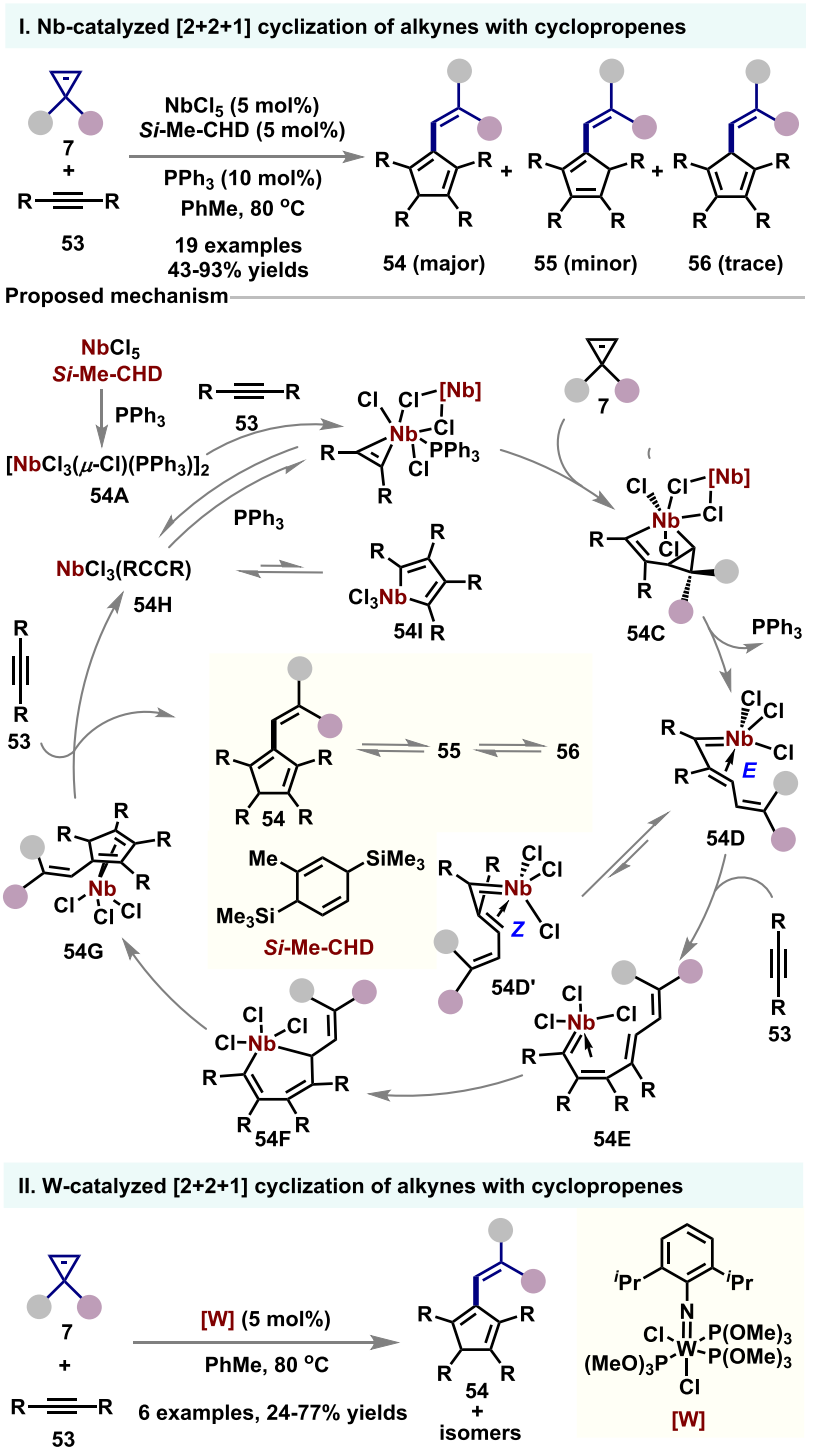
Scheme 20. Cyclization of Alkynes with Cyclopropenes *via* [2 + 2 + 1] Cascade



2.4. Cascade Vinylcarbeniod Transformations Involving Ylide Formation

Carbene chemistry involving ylide formations constitute a fundamental paradigm in modern organic synthesis, operating through a concerted tandem of carbene generation, nucleophilic attack, and subsequent diversification of the transient ylide intermediates.[94] This strategy elegantly converts the inherent reactivity of carbenes into versatile building capacity, serving as an indispensable tool for constructing C−C/C−X bonds, accessing cyclic architectures, and enabling skeletal rearrangements.[95] While conventional approaches rely on diazo-derived carbenes that undergo metal-assisted polarity inversion to form electrophilic metal-carbene complexes—readily captured by heteroatoms (O, N, S) to generate corresponding ylides—recent advances have unveiled the unique utility of cyclopropene-derived vinyl carbenes in this cutting-edge area. These intermediates can be trapped by nucleophilic sites to form ylide species, with the vinyl moiety often playing a critical role in subsequent transformations.[96]

The Hu group has established a systematic framework for ylide chemistry using cyclopropane as carbene precursors. In

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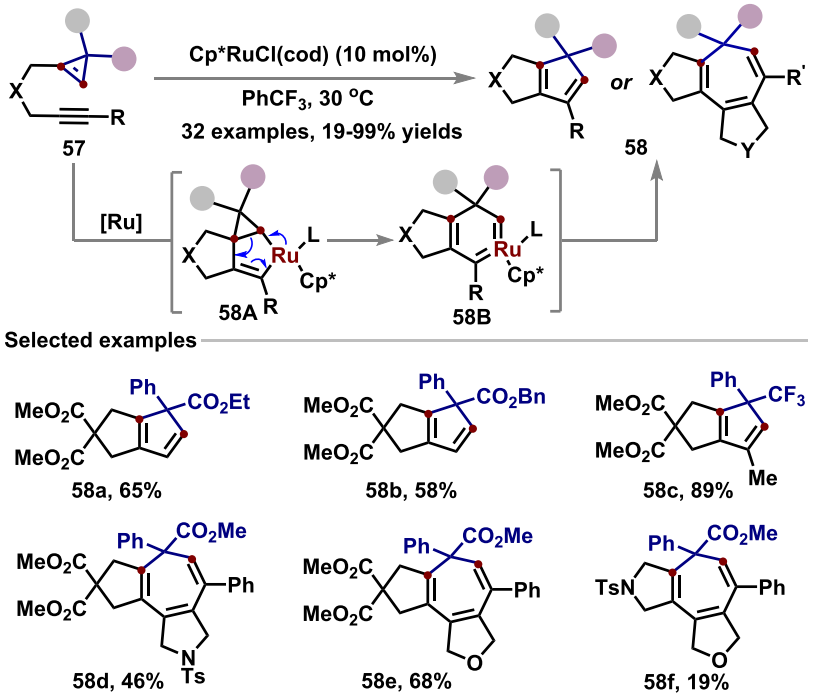
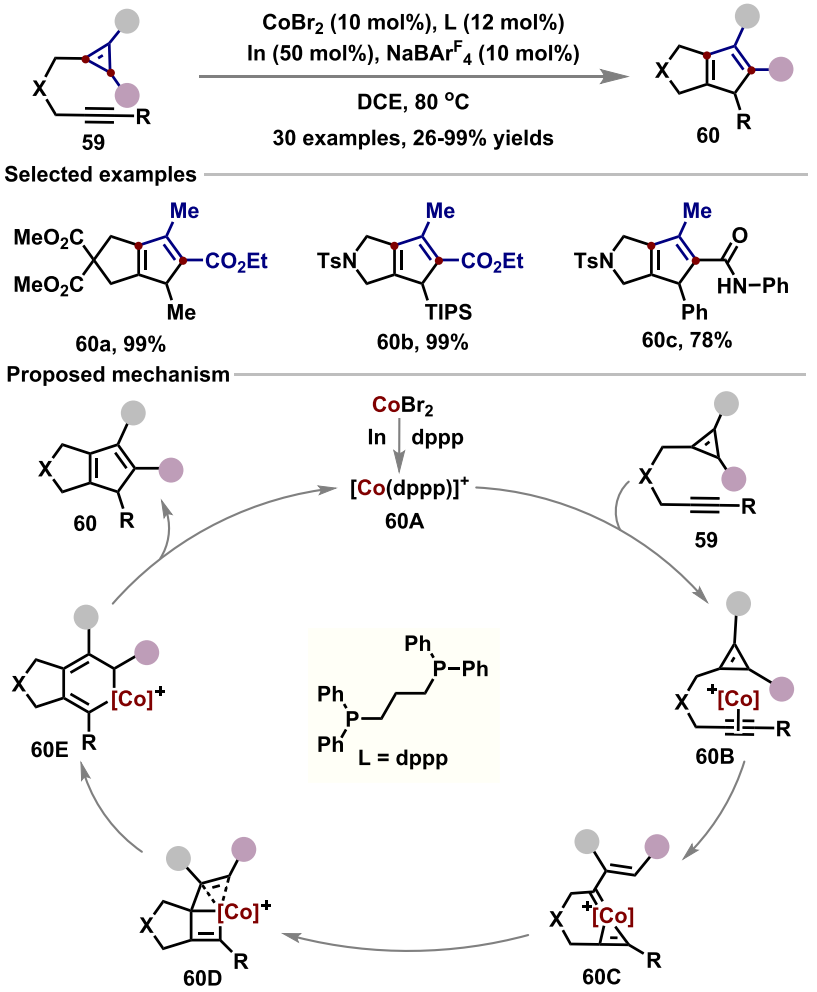
Scheme 21. Ru-Catalyzed Intramolecular [3 + 2] Annulation of Alkynes with Cyclopropenes



Scheme 22. Co-Catalyzed Intramolecular [3 + 2] Annulation of Alkynes with Cyclopropenes



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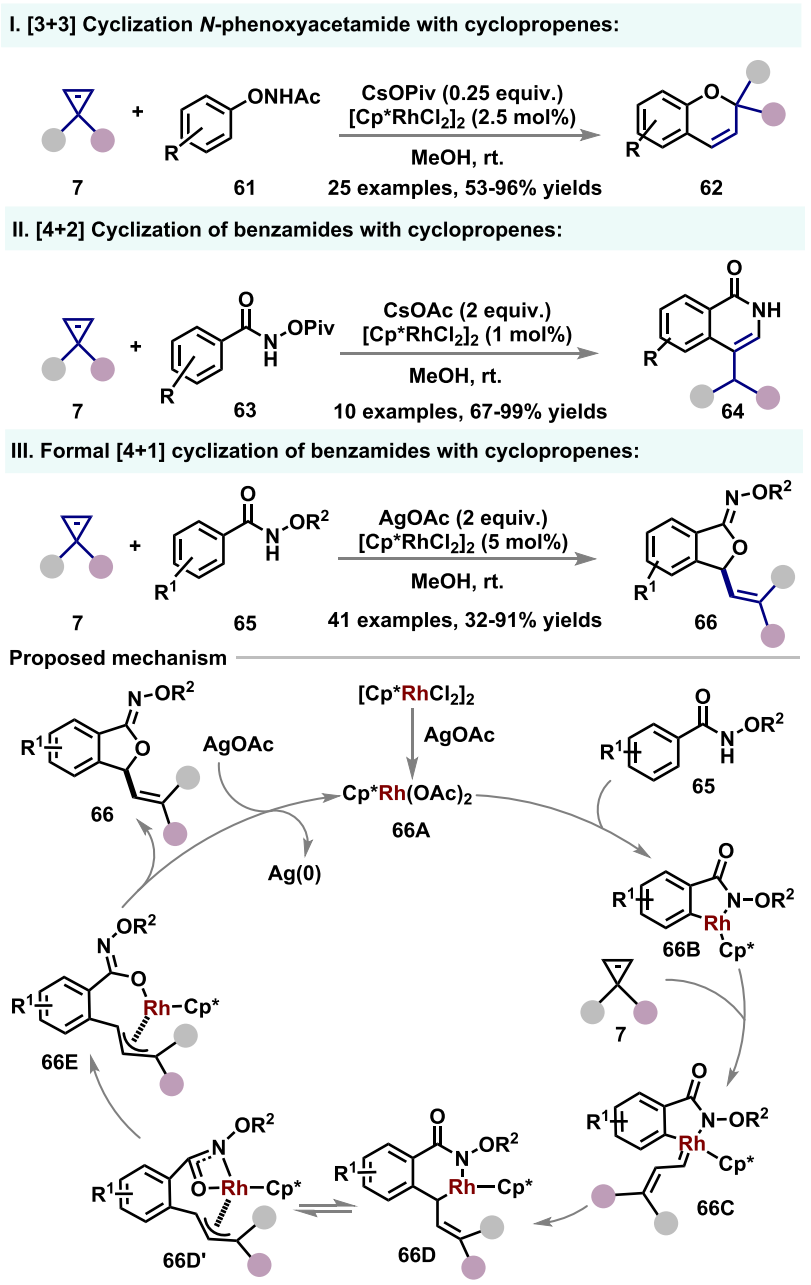
Scheme 23. Rh(III)-Catalyzed Cyclization of Cyclopropenes *via* C−H Activation



2019, They described a rhodium(II)-catalyzed aldol-type reaction between cyclopropene alcohols **70** and isatins **71** (Scheme 25, **I**).[97] The transformation proceeds through ring-opening to vinyl carbene **72A**, intramolecular oxygen trapping to form key oxonium ylide **72B**, and nucleophilic addition to afford hydroxyoxindole derivatives **72**. Notably, due to the retro-aldol reaction of hydroxyoxindole derivatives during silica chromatography isolation, compounds **72a** and **72b** were obtained in moderate yields with low diastereoselectivity. To obtain stable products, a one-pot methylation using MeI/NaH was conducted, affording the stabilized product. This reaction tolerated various substituents (e.g., chloro, methoxy) at different positions on the isatin aromatic ring, giving the corresponding stable derivatives in moderate yields (**72c**−**72d**). Addressing the challenge of carboxylate-stabilized ylides—where proton transfer compromises stability—the group employed cyclopropene carboxylic acids **73** as bifunctional precursors (Scheme 25, **II**).[96] Rhodium catalysis enables ring-opening to carbene **74A**, followed by cyclization to cyclic oxonium ylide **74B**. The conjugated system enhances stability while facilitating nucleophilic addition to isatin **71**, affording spirocyclic γ-butenolide-oxindoles **74**. Notably, the group recently extended this strategy to earth-abundant copper catalysis (Scheme 25, **III**).[98] Copper-promoted ring-opening/cyclization generates analogous oxonium ylides that undergo Michael addition with isatin-derived malononitriles **75**, enabling stereoselective synthesis of 3,3-disubstituted oxindoles **76**. The system exhibits broad functional group tolerance, accommodating diverse isatin derivatives (**76a**−**76b**) and structurally modified cyclopropene carboxylic acids **76c**.

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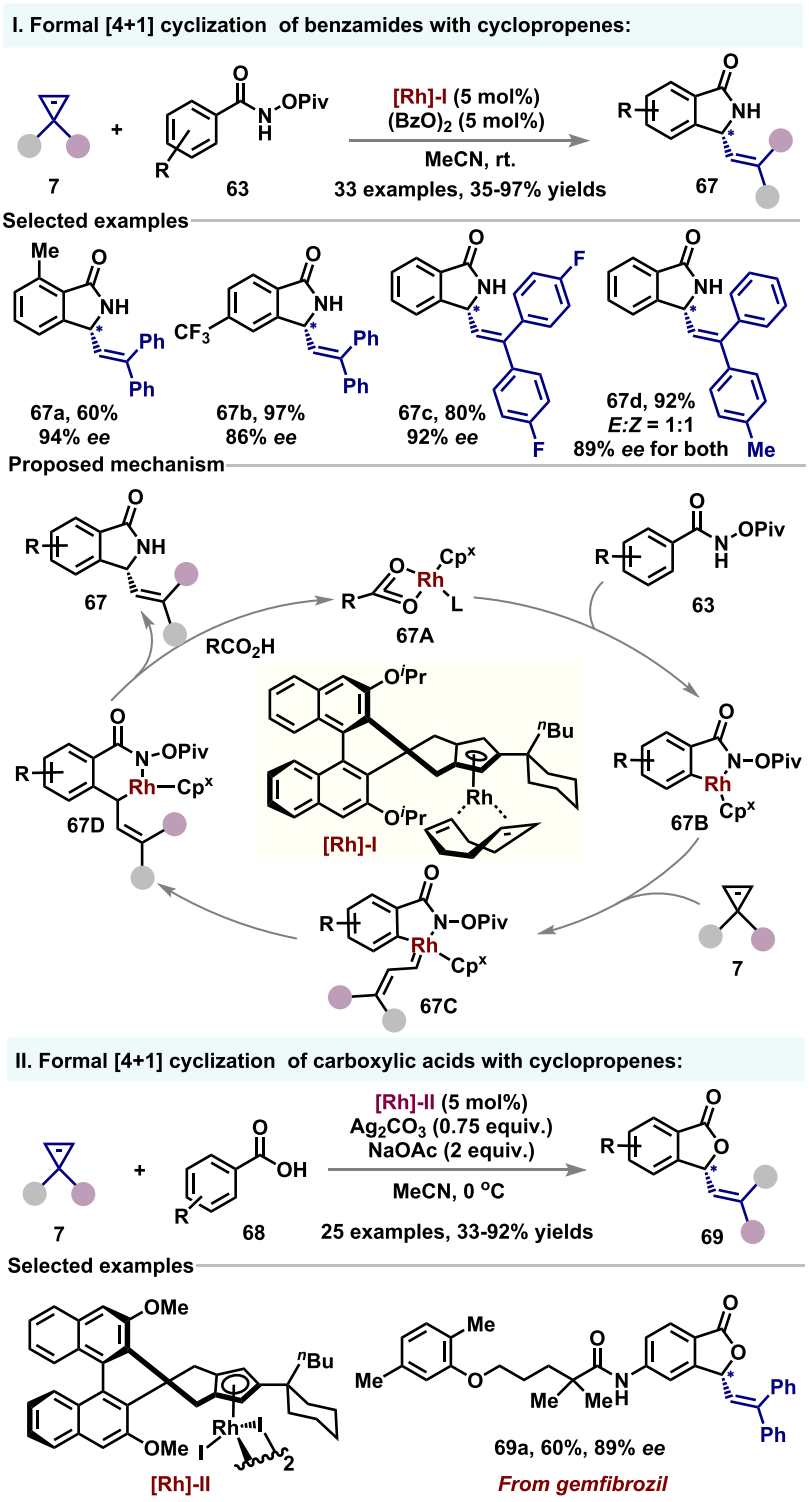
Scheme 24. Rh(III)-Catalyzed Asymmetric [4 + 1] Cyclization of Cyclopropenes



In 2020, the Hu group extended their ylide methodology to include rhodium(II)-catalyzed reactions between cyclopropene carboxylic acids **73** and conjugated alkenes **77**, achieving the synthesis of γ-butenolides **78** *via* Michael addition to transient carboxylate-stabilized oxonium ylides (Scheme 26, **I**).[99] Despite extensive screening, chiral rhodium catalysts failed to induce enantioselectivity, suggesting the chiral catalyst may not participate in the stereodetermining nucleophilic addition step. To address this stereocontrol challenge, the same group subsequently developed a cooperative catalytic system including $Rh_2(esp)_2$ and a chiral phosphoric acid (CPA), enabling asymmetric addition of cyclopropene carboxylic acids **73** to imines **79** (Scheme 26, **II**).[100] In this catalytic system, the CPA serves a dual role: activating the electrophilic imine while directing stereoselective attack on the oxonium ylide through its chiral confined environment, affording chiral γ-butenolides **80** with excellent enantioselectivity. The methodology exhibits broad

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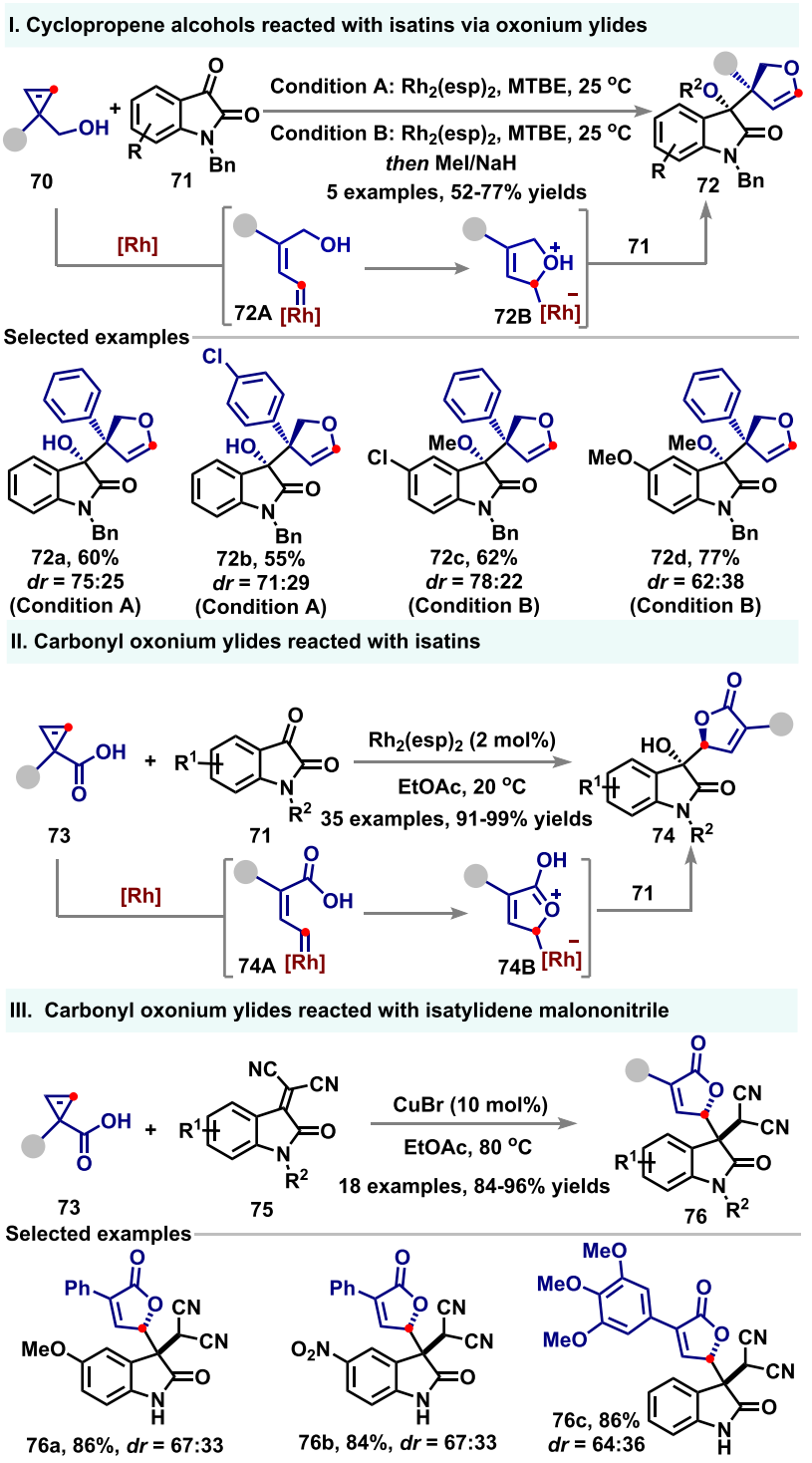
Scheme 25. Metal-Induced De Novo Umpolung of Vinylcarbene Reactivity



functional group tolerance, accommodating halogenated and strongly electron-deficient (CF_3, NO_2) imines to furnish products (**80a**–**80c**) with high efficiency and stereoselectivity. Significant practical utility was demonstrated through the late-stage diversification of a cyclopropene carboxylic acid derived from isoxepac, delivering pharmaceutically relevant γ-butenolide **80d** with 55% yield and 92% *ee*. Mechanistic analysis reveals a sequence involving rhodium-catalyzed ring-opening to vinyl carbene **80A**, intramolecular cyclization to oxonium ylide **80B**, and tautomerization to the key 3-aryl-2-hydroxyfuran intermediate **80C′**. The CPA-organized transition state **80D** then directs stereoselective C–C bond formation between the nucleophilic species and the activated imine **80E**, culminating in the enantiomerically enriched product.

In 2023, the Hu group advanced their ylide trapping methodology to a three-component system, achieving one-pot assembly of polysubstituted γ-butenolides **83** through interception of rhodium-generated carboxylate-oxonium ylides with *in situ* formed α,β-unsaturated iminium ions (Scheme

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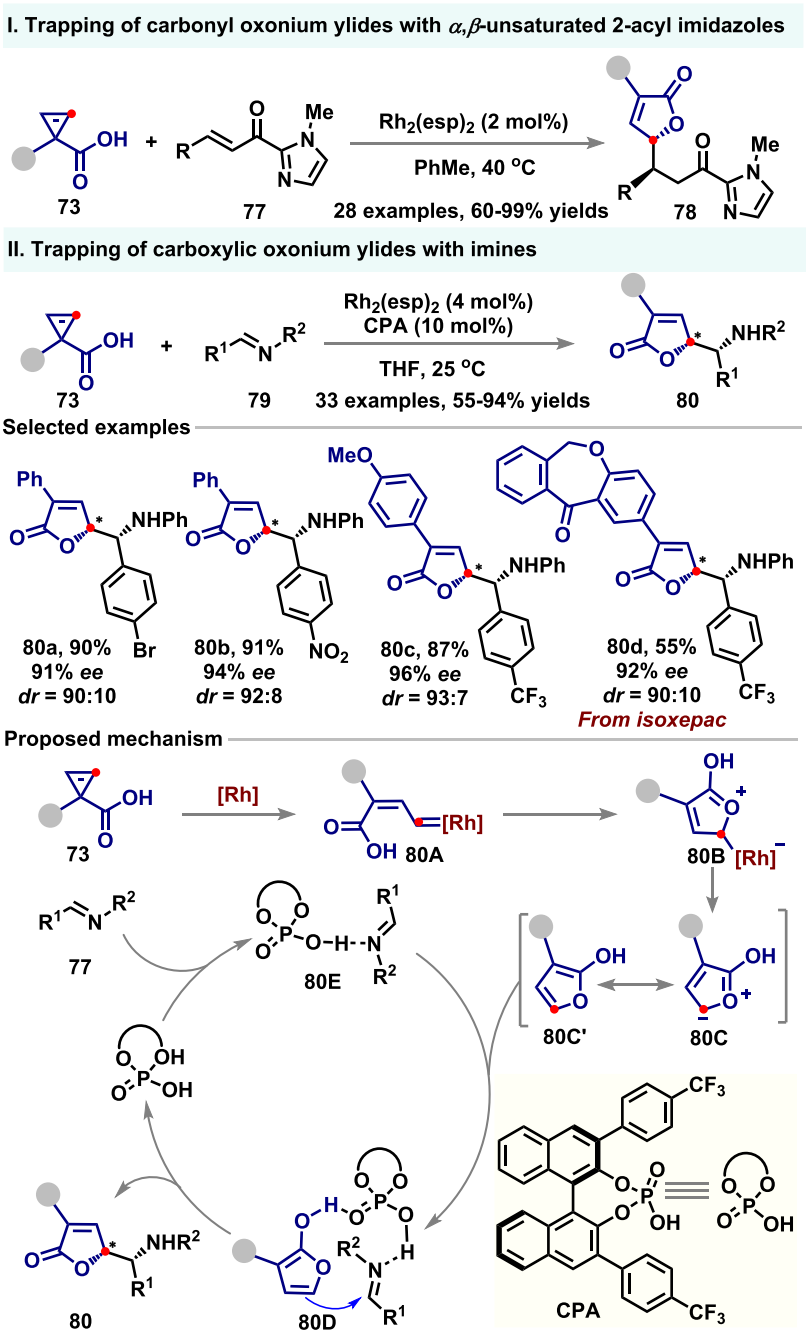
Scheme 26. Trapping of Carbonyl Ylides with Alkenes and Imines



27).[101] The transformation exhibits notable steric and electronic effects: *ortho*-substituted cyclopropenes enhance diastereocontrol **83a**, while aliphatic and electron-deficient aldehydes give moderate yield (**83b**, 50%) due to iminium formation challenges. Alkyl-substituted enamines show reduced efficiency **83c** due to decreased iminium stability. Mechanistically, copper-catalyzed ring-opening generates oxonium ylide **83B**, equilibrating with resonance form **83C′**. Competitive proton transfer leads to byproduct **83D**, while the major pathway involves interception by iminium **83E** (from aldehyde **81**/enamine **82** condensation) to form adduct **83F**, followed by hydrolysis to **83**. This multicomponent approach effectively suppresses competing carbene and ylide pathways, though asymmetric induction remains unexplored.

The Hu group developed cyclopropenes with nucleophilic substituents that undergo intramolecular cyclization to oxonium ylides, which are trapped by electrophiles to form γ-butenolide derivatives. Cyclopropene **7** can also react with intermolecular nucleophiles to form ylide intermediates, which participate in further carbene transformation reactions. In 2022, Sun's group utilized cyclopropene **7** as a carbene precursor with pyridine-2- carboxylates to form pyridinium ylides, which undergo dearomative rearrangement to *N*-alkylated 2-pyridones **85** (Scheme 28, **I**).[102] The tetrakis[*N*-phthaloyl-(*R*)-*tert*- leucinate]dirhodium ($Rh_2(PTTL)_4$)-catalyzed reaction proceeds through vinyl-rhodium carbene **85A**, nucleophilic attack by 2- hydroxypyridine **84** gives ylide **85B**, and intramolecular cyclization yields intermediate **85C**. C−O bond cleavage and dearomatization then afford product **83**

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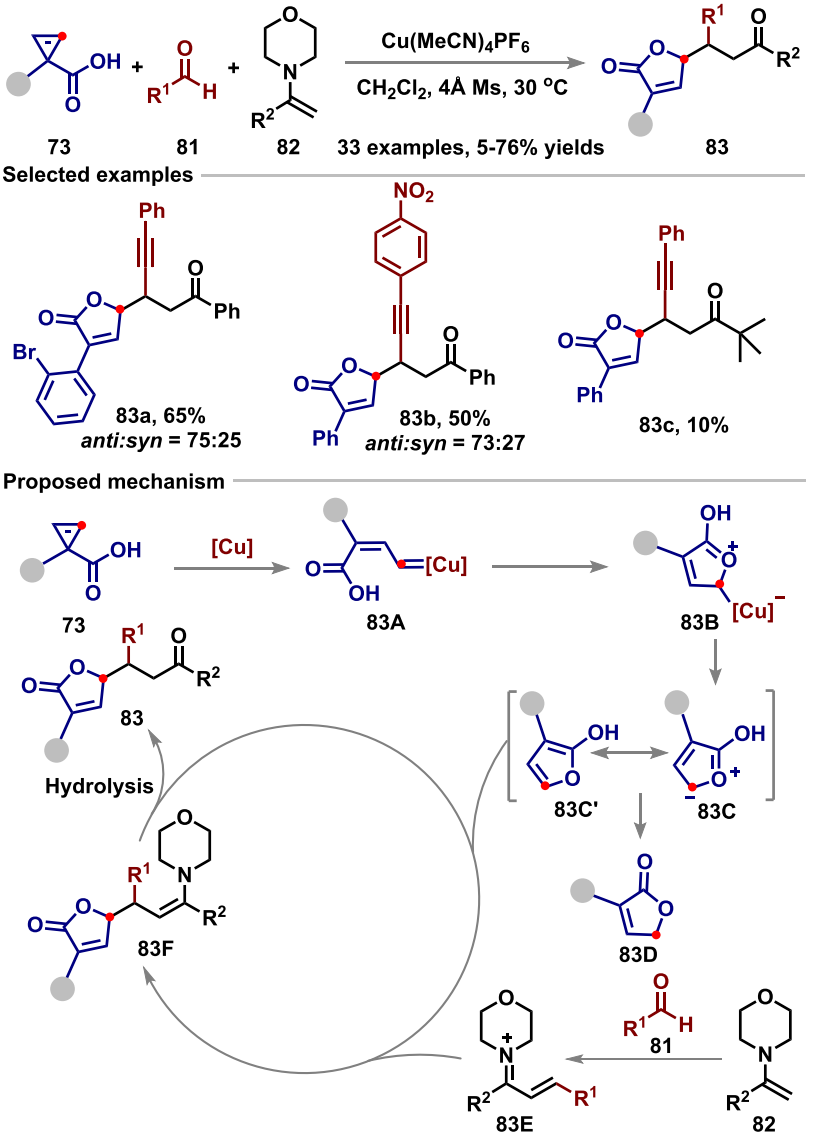
Scheme 27. Trapping of Ylide Intermediates in Multi-Component Reactions



with catalyst regeneration. In 2024, the same group expanded this approach by incorporating sulfonyl groups to access bifunctional compounds **87** while forming C(sp^3)−N and C(sp^3)−SO_2R bonds (Scheme 28, **II**).[103] The reaction proceeds *via* a metal-bound nitrogen ylide, with DFT calculations supporting a five-membered transition state for Rh-ketene-enol tautomerization that enables sulfonyl migration. This mild, practical system tolerates diverse substrates (**87a**−**87d**) but shows poor stereoselectivity with asymmetric cyclopropenes.

Cyclopropene-derived vinyl carbenes and their *in situ* generated pyridinium ylides represent highly reactive intermediates, though their electrophilic trapping typically requires a terminal hydrogen on the ylide to facilitate proton transfer. In 2023, Hu's group devised 2-*O*-Boc-pyridines to enable multicomponent reactions with terminal hydrogen-free pyridinium ylides (Scheme 29).[104] They introduced a delayed aroylation strategy that avoids competing intramolecular acyl transfer by postponing the acyl migration step. Using cyclopropenes as carbene precursors, this method achieves highly selective synthesis of polysubstituted conjugated indoles **89** through a cascade coupling with *O*-Boc-pyridine **88** and isatin **71** *via* a sequential delayed aroylation−elimination process. The reaction exhibits broad substrate scope. *Para*- or *meta*-halogen substituted aryl methoxy cyclopropenes gave excellent yields (**89a**, **89b**), while *ortho*-substituted substrates showed lower yields due to steric effects **89c**. Methyl groups at pyridine 3- or 5-positions were well tolerated (**89d**, **89e**), and unprotected isatin provided the product in 96% yield (**89f**). The proposed mechanism involves: $Rh_2(OAc)_4$-catalyzed cyclopropene ring opening to vinyl−rhodium carbene **89A**; pyridine nucleophilic attack forming ylide **89B**; isatin carbonyl addition giving **89C**; 1,4-acyl migration *via* seven-membered transition state **89D** to give **89E**; and final BocOH elimination to form product **89**.

2.5. Miscellaneous Transformations of Cyclopropenes

In recent years, vinyl carbene intermediates generated through cyclopropene ring-opening have emerged as versatile platforms for constructing polysubstituted 1,3-dienes *via* intramolecular isomerization strategies. In 2009, Wang and co-workers reported a gold-catalyzed isomerization of carboxylic acid-derived cyclopropenyl esters **90**, which

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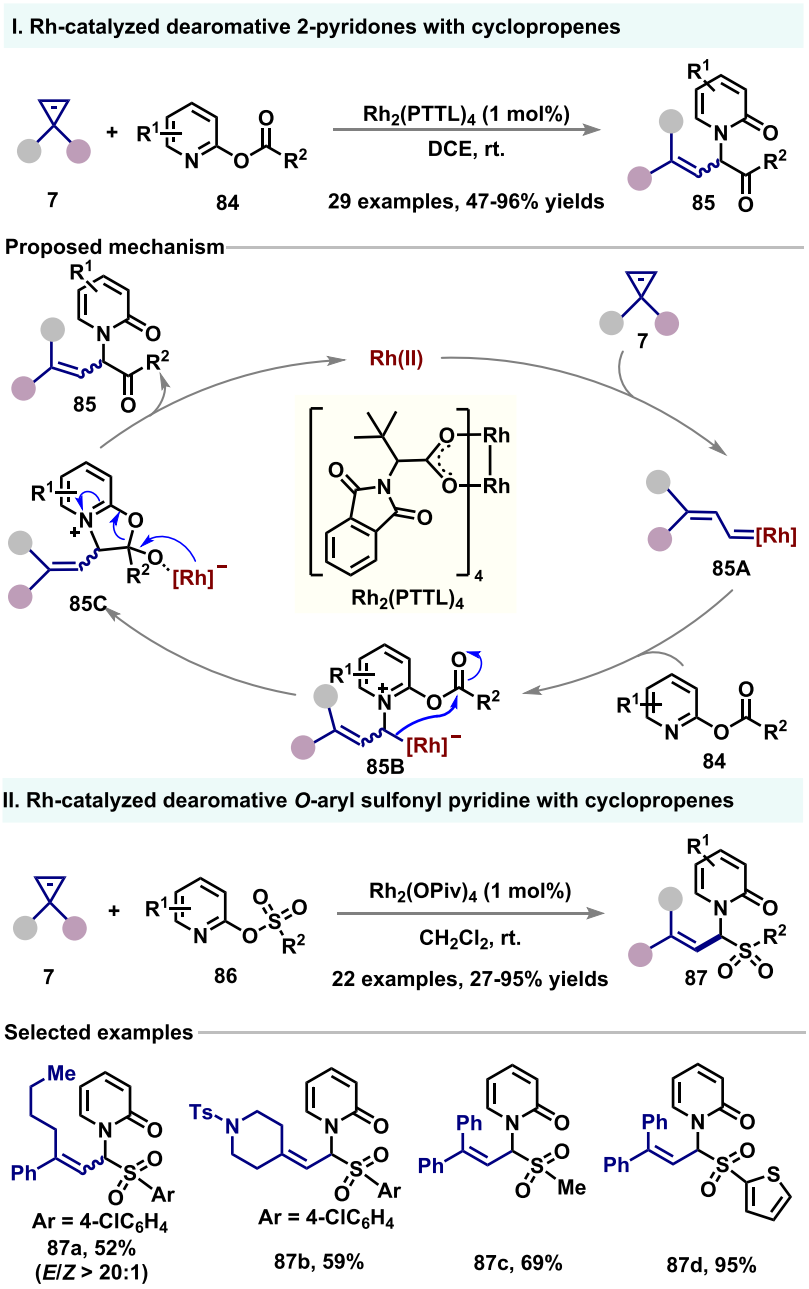
Scheme 28. Rh-Catalyzed Dearomative Rearrangement of 2-Oxypyridines with Cyclopropenes



proceeds *via* a gold vinyl carbene complex (Scheme 30, **I-A**).[105] Under promotion by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the intermediate undergoes intramolecular aromatic C−H insertion followed by elimination, affording indene derivatives **91** bearing a 1,3-diene moiety in high efficiency. In 2010, Hyland et al. designed methyl-substituted cyclopropenyl acetate **92** and systematically explored its gold-catalyzed isomerization, successfully accessing 1,3-diene derivatives **93** with *Z*-stereoselectivity (Scheme 30, **I−B**).[106] Combining experimental studies with DFT calculations demonstrated the involvement of a vinyl gold carbene intermediate and further elucidated the origin of the stereoselectivity.

Although metal-catalyzed cyclopropene isomerization has proven highly effective for constructing multifunctionalized 1,3-dienes, the introduction of hydroxyl groups into conjugated systems to afford 1,3-dienol derivatives remains challenging due to competing O−H insertion pathways. In 2024, the Waser group designed cyclopropenol substrate **94** and achieved efficient synthesis of polysubstituted 1,3-dienol derivatives **95** under mild platinum catalysis (Scheme 30, **II**).[107] This catalytic system accommodates diverse functional groups. Substrates bearing methoxy or bromo substituents on the aryl ring delivered the target products in 50% and 62% yields, respectively (**95a**, **95b**). Hydroxyl-protected substrate was also converted to the corresponding 1,3-diene **95c** in 77% yield, indicating that a free hydroxyl group is not essential for the transformation. The method was further applied to cyclopropene substrates derived from the natural product citronellal **95d**, underscoring its potential in synthetic applications. A plausible reaction pathway was proposed. Initial coordination of the platinum catalyst to the C═C

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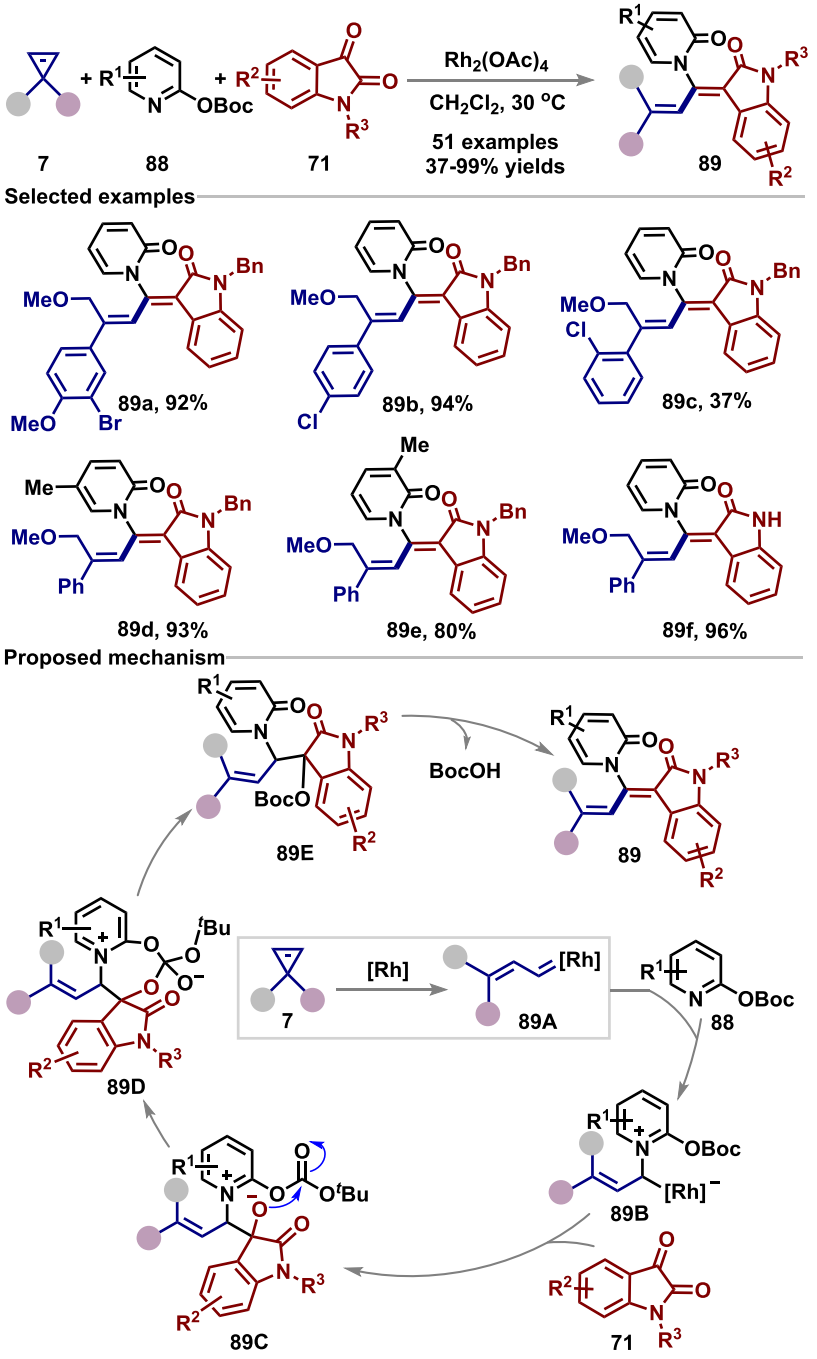
Scheme 29. Multicomponent Reaction Synthesis of Conjugate Oxindoles Involving Pyridinium Ylides



bond of cyclopropenol **94** forms π-complex **95A**, which undergoes ring-opening to afford the key vinyl−platinum carbenoid **95B**. Subsequent [1,5]-H migration yields platinum hydride species **95C** (Path A). Alternatively, direct metal insertion into the cyclopropene could generate metallacyclobutane intermediate **95D**, which may either open to **95B** (Path B) or undergo β-hydride elimination to directly furnish **95C** (Path C). Finally, reductive elimination from **95C** releases the 1,3-diene product **95** and regenerates the platinum catalyst.

In 2022, Xie's group developed a gold-catalyzed intramolecular rearrangement of diester-substituted cyclopropene **96** to selectively access polysubstituted naphthols **97** by fine-tuning the electronic properties of the gold center (Scheme 31).[108] Ligand and counterion optimizations revealed that the chemoselectivity is controlled by the electron density at gold. The reaction tolerates diverse substituents on the arene ring (alkyl, halogen, methoxy), generating naphthols (**97a**−**97c**) in moderate yields. A naphthyl-substituted substrate gave phenanthrene **97d** with high regioselectivity, and 3-thienyl or varied ester groups were also compatible (**97e**−**97f**). Strong electron-withdrawing groups suppressed reactivity. Mechanistically, LAu^+ coordinates to the C=C bond of **96** to form **97A**, which undergoes selective C−C cleavage to give a resonance hybrid of carbocation **97B** and gold carbene **97C**. Cyclization gives **97D**, followed by 1,2-acyl migration to ketene **97E**. Intramolecular Friedel−Crafts attack then furnishes naphthalene **97**. Experimental data indicate that

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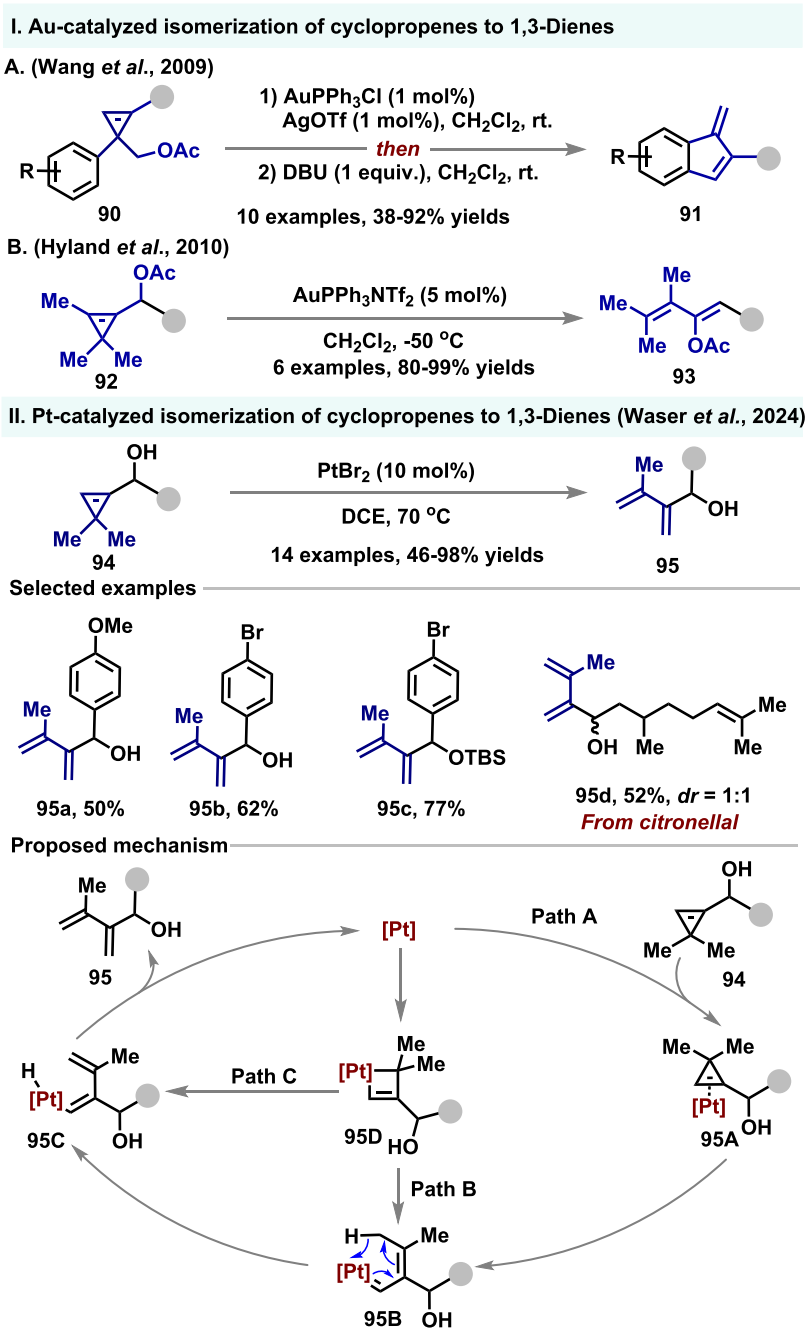
Scheme 30. Metal-Catalyzed Isomerization of Cyclopropenes to 1,3-Dienes



electron-rich ligands enhance π-donation, stabilizing the gold carbene and promoting product formation.

Diazo compounds themselves can serve as nucleophiles, with the terminal nitrogen atom selectively attacking electrophilic carbene precursors.[109] In 2021, Liu and co-workers disclosed a gold-catalyzed C−N coupling between α-diazonitriles **99** and cyclopropenes **98** to deliver polysubstituted (*E*)-2,3-diaza-1,3,5-hexatrienes **100** through an *N*-attack manifold (Scheme 32).[110] The transformation demonstrates broad substrate generality. Cyclopropenes bearing aryl, naphthyl, or heteroaryl groups reacted smoothly (**100a**−**100c**). A 3-thienyl substrate gave **100c** in 76% yield with >25:1 *E*/*Z* ratio. Various *meta*-, and *para*-substituted α-aryl diazonitriles were also compatible (**100d**−**100e**). Mechanistically, gold-catalyzed cyclopropene ring-opening affords vinyl gold carbene **100B**, which undergoes nucleophilic attack by the terminal nitrogen of **99**. The resulting intermediate **100C** then undergoes proton transfer and isomerization to furnish product **100**. The strong electron withdrawing cyano group stabilizes the nitrogen anion in resonance form **99′** effectively controlling the reaction selectivity.

The sulfonyl group is widely present in pharmaceuticals, agrochemicals, and functional materials, where it significantly modulates biological activity and enhances material properties.[111] Traditional methods for sulfonyl compound synthesis often require strong oxidants, leading to poor functional group tolerance; direct insertion of gaseous SO_2, on the other hand, suffers from toxicity and handling difficulties.[112] Recently, Lin and co-workers developed a copper-catalyzed

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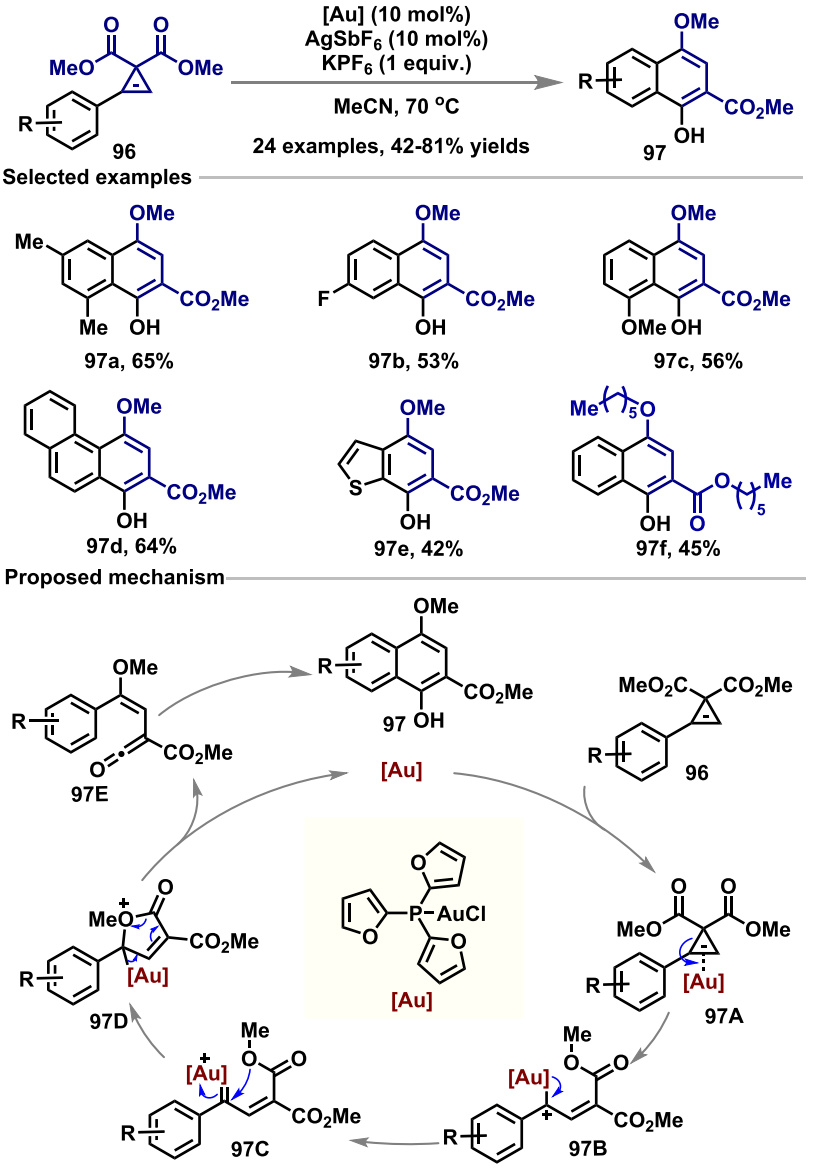
Scheme 31. Au-Catalyzed Rearrangement of Cyclopropenes to Naphthols



ring-opening/sulfonylation of cyclopropenes **7** using *β*-thioamide sulfones **101** as reliable sulfonyl sources (Scheme 33).[113] The reaction tolerates electron-donating groups **102a**, sterically hindered *ortho*-aryl and cyclohexyl substituents (**102b**−**102c**), as well as electron withdrawing, heterocyclic, and fused ring sulfonyl moieties (**102d**−**102f**). However, the stereoselectivity of the resulting alkene remains challenging to control. A proposed catalytic cycle involves: reduction of $CuCl_2$ by the sulfone/DBU to Cu(I) species **102A**; S−Cu(I) coordination forming **102B**; cyclopropene ring opening to vinyl copper carbene **102C**; nucleophilic addition to give **102D**; and retro Michael elimination/protonation delivering sulfone **102** with catalyst regeneration. This method offers a straightforward route to allylic aryl sulfones, highlighting potential utility in drug and material synthesis.

Palladacycles are regarded as key intermediates in catalytic cycles, yet the synthesis and systematic study of their isolable forms remain relatively limited.[114] Recently, the Jiang group successfully constructed a series of isolable palladacyclic intermediates, unequivocally characterized by X-ray diffraction, by integrating cyclopropenes as donor-type carbene precursors with a Pd(II)-catalyzed inert C(sp^3)−H activation strategy (Scheme 34).[115] The reaction exhibits broad substrate scope. Linear alkyl chains gave high yields **104a**, while naphthyl substrates afforded **104b** with excellent enantioselectivity. Late-stage functionalization of drugs such as naproxen and ibuprofen were also achieved **104c** and **104f**. Symmetric alkyl substituted cyclopropenes provided **104d** in 74% yield, whereas an acetate-substituted derivative exhibited a unique weak-coordination effect, delivering the product in 95% yield with high selectivity as a single isomer **104e**. A plausible mechanism is proposed: initial C−H activation at the *β*-position of the amide, directed by the 8-aminoquinoline auxiliary, affords Pd(II) species **104A**. Coordination with the cyclopropene forms *π*-complex **104B**, which undergoes ring-opening to generate the key vinyl−palladium carbene intermediate **104C**. Final 1,1-migratory insertion then forges the C−C bond. Notably, catalytic turnover *via* Pd elimination was not achieved.

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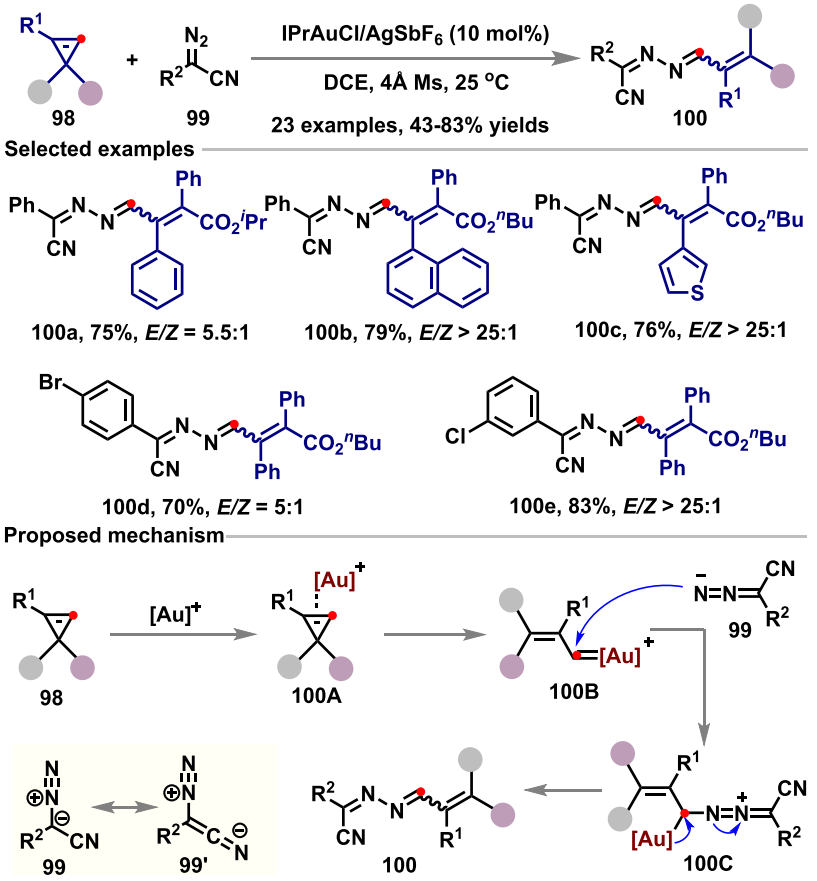
Scheme 32. Au-Catalyzed Synthesis of Diaza-1,3,5-hexatrienes from Cyclopropenes and Diazos



3. STRAIN-RELEASE RING OPENING OF BICYCLO[1.1.0]BUTANES TO GENERATE ALLYLCARBENES

Bicyclo[1.1.0]butane (BCB), a highly strained bicyclic scaffold formed by two fused cyclopropane rings sharing a central C−C bond, exhibits unique structural and electronic features.[116] The central bridge bond (~1.46−1.50 Å) resembles the outer C−C bonds in length, while the interplanar angle between the cyclopropane units is about 123°. With a strain energy of approximately 66 kcal/mol—significantly higher than the sum of two isolated cyclopropanes—BCB is a thermodynamically activated system that displays diverse reactivity patterns.[117] Although BCB's unique structure and high ring strain had been recognized early on, its synthesis was first achieved by Wiberg and co-workers in 1959 *via* dehalogenative elimination of ethyl 3-bromocyclobutane-1-carboxylate using sodium triphenylmethylide.[118] In 2011, Sulikowski et al. successfully incorporated a BCB fragment in the total synthesis of a natural bicyclobutane fatty acid.[119] The strained central C−C bridge, characterized by distorted bond angles and unusual bond lengths, confers thermodynamic instability and diverse reactivity.[117] The central σ-bond possesses pronounced π character, enabling reactions with nucleophiles, electrophiles, and radicals to deliver polysubstituted cyclobutanes.[120] Additionally, BCBs participates in cycloadditions with C═X (X = C, N, O) partners to access three-dimensional (3D) scaffolds such as bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.1.1]hexanes (BCHs), and bicyclo[4.1.1]octanes (BCOs),[12] supporting "escape from flatland" strategies in medicinal chemistry.[121] Insertion reactions with carbenes further afford skipped dienes and BCP derivatives, collectively establishing BCB as a versatile building block in contemporary synthesis.[122]

Notably, BCBs can undergo ring opening isomerization under transition metal catalysis (e.g., Ni, Rh) to generate a distinctive allylic type carbene precursors. In 1971, Noyori and co-workers reported that BCB **105** undergoes cyclopropanation with alkenes such as acrylate **106** in the presence of bis(acrylonitrile)nickel(0) ($Ni(AN)_2$) to furnish allyl substituted cyclopropanes **107** (Scheme 35, I).[123] Both unsubstituted and alkyl-substituted BCBs reacted efficiently, with the latter affording products in good yields and stereoselectivity (**107a**−**107c**). Mechanistically, nickel(0) is proposed to insert into the central C−C bond, leading to isomerization into a nickel allyl carbene intermediate **107A** or its ionic resonance forms **107B** and **107C**, which subsequently undergo typically carbene cyclopropanation. Noyori group later employed valence bond and molecular orbital theories to elucidate the electronic structure and resonance behavior of carbenes bound to transition metal complexes.[124] The bonding was described as a σ donation from the carbene sp^2 lone pair to a metal vacant orbital, complemented by π-backdonation from metal *d*-orbitals into the carbene empty *p*-orbital. This π-backdonation stabilizes the ylide form **107B** while suppressing the cationic contributor **107C**, rendering the intermediate nucleophilic and susceptible to trapping by electron deficient alkenes. In 1981, Noyori and colleagues further systematically investigated the stereospecific trapping of nickel allylic carbenoids through deuterium labeling and stereochemical analysis,[125]

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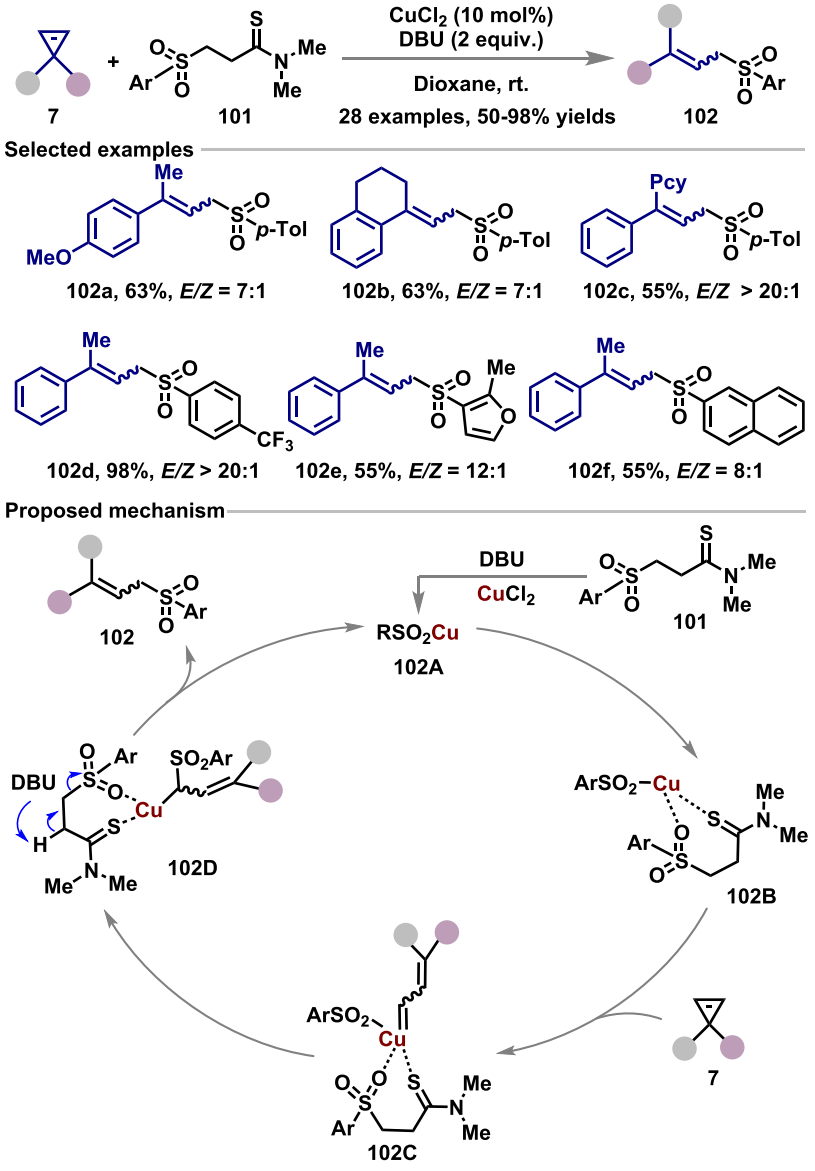
Scheme 33. Cu-Catalyzed Sulfonylation of Cyclopropenes



confirming that Ni(0) catalyzed cleavage of the central bridge and a specific peripheral C−C bond generates a nucleophilic nickel carbene complex that undergoes highly stereospecific *cis*-cyclopropanation with electron deficient alkenes.

Parallel studies by Gassman et al. revealed that Rh(I) complexes promote the rearrangement of BCBs **108** to give both diene **109** and vinylcyclopropane **110**, the latter arising *via* intramolecular cyclization of a putative rhodium carbene intermediate (Scheme 35, II).[126] Intermolecular trapping experiments with electron poor alkenes furnished cyclopropanes **112**, while electron rich alkenes remained unreactive—consistent with the intermediacy of a nucleophilic metal stabilized carbene. Although these pioneering studies laid the conceptual groundwork, the field remained relatively unexplored for decades. Recent advances in BCBs synthesis and a growing appreciation of its value as a modular carbene precursor have now spurred renewed investigation. The following section highlights progress in leveraging BCB as a carbene source for the construction of functional molecules.

Early studies by Noyori and co-workers primarily focused on transition metal catalyzed cyclopropanation of alkenes using BCBs as a carbene precursor, with experimental evidence confirming the involvement of carbene intermediates. However, these transformations were largely limited to electron-deficient alkenes and offered narrow synthetic versatility, leading to a prolonged period of limited progress in the field. In 2008, the Wipf group reported a rhodium(I)-catalyzed ring-opening rearrangement of BCB that, through a ligand-controlled intramolecular cyclopropanation, enabled the selective construction of azabicyclo[3.1.0]hexane frameworks, thereby expanding the utility of BCBs as a carbene precursor in organic synthesis (Scheme 36).[127] In this Rh(I)/phosphine ligand system, the monodentate ligand PPh_3 favored the formation of pyrrolidine **114**, while the bidentate ligand 1,2-bis(diphenylphosphino)ethane (dppe) preferentially led to azepane **115**. The method displayed good functional group tolerance, with various aromatic groups (**114a, 115a**) and heteroaryl substituted substrates (**114b, 115b**) undergoing efficient conversion. A mechanistic proposal involves initial oxidative addition of Rh(I) into the

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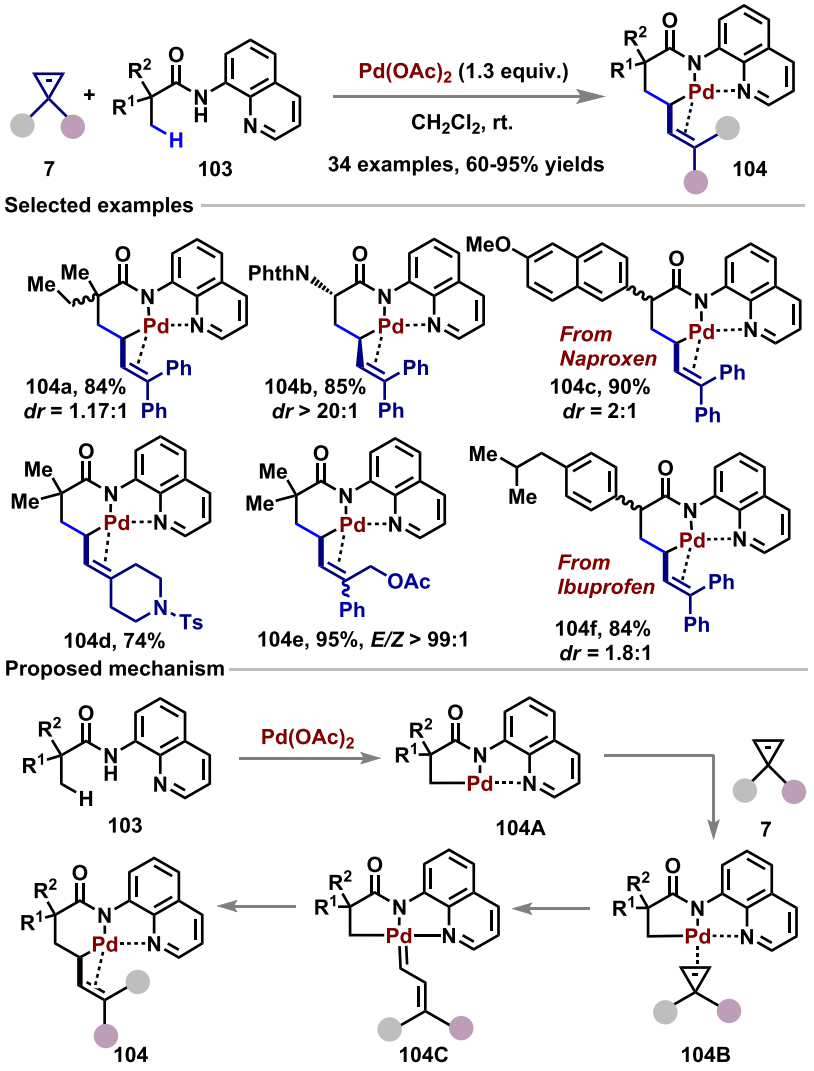
ACS Catal. 2026, 16, 3013−3071

Scheme 34. Palladacycle Construction *via* Ring-Opening of Cyclopropenes



central C−C bond of BCB, generating tricyclic rhodacycle **114A**. Subsequent ligand-dependent rearrangement then delivers two distinct metal-carbene intermediates: with PPh_3, proximal carbene−Rh complex **114B** forms and undergoes intramolecular cyclopropanation to give pyrrolidine **114**; with dppe, distal carbene−Rh species **114C** is generated and leads to azepane **115**. In 2022, the same team provided deeper mechanistic insight through comprehensive DFT calculations.[128] The results revealed that in the PPh_3 system, the central σ-bond of BCB undergoes concerted cleavage of two C−C bonds to form a rhodium allylic carbene intermediate, affording the trans configured pyrrolidine product. In contrast, with the dppe ligand, steric control directs the selective formation of the *cis*-azepane.

The "escape from flatland" concept in modern medicinal chemistry emphasizes replacing planar aromatic rings with three-dimensional molecular scaffolds as bioisosteres to improve physicochemical and pharmacological properties.[121] In recent years, BCB has emerged as a key three-dimensional synthon, with its cycloaddition chemistry enabling important advances in the construction of C(sp^3)-rich polycyclic frameworks.[12] Building upon their earlier studies,[129] the Wipf group in 2024 reported a Rh(I)-catalyzed intramolecular isomerization/cyclization of BCB-derived substrates, accessing complex three-dimensional polycycles that are challenging to synthesize by other methods (Scheme 37).[130] The strategy begins with nucleophilic addition of a metal substituted BCB reagent to quinoline- or pyridine-derived iminium salts, generating *in situ* a series of BCB-functionalized dihydroquinoline intermediates. Without isolation, these intermediates undergo a rearrangement/cyclization cascade under catalysis by chlorodicarbonylrhodium dimmer ($[Rh(CO)_2Cl]_2$)/dppe in 1,4-dioxane at 120 °C, furnishing rigid 1-methylene-5-azacyclopropa[*cd*]indene scaffolds **119** or **123**. This "one pot, two step" process exhibits excellent functional group tolerance, accommodating sensitive groups such as trifluoromethyl, nitro, hydroxy, and amide to afford products **123a−123d**. Mechanistic studies and DFT calculations support a pathway involving initial coordination of Rh(I) to the olefin of the substrate, forming π-complex **119A**. This is followed by concerted cleavage of two C−C bonds in the BCB core to generate the key rhodium carbene intermediate **119B**. Subsequent [2 + 2] cycloaddition of **119B** with the adjacent olefin yields metallacyclobutane **119C**, which undergoes reductive elimination to release the product **119** and regenerate the rhodium catalyst. This work expands the utility of BCB chemistry in the synthesis of fused heterocycles, and the resulting 1-methylene-5-azacyclopropa-

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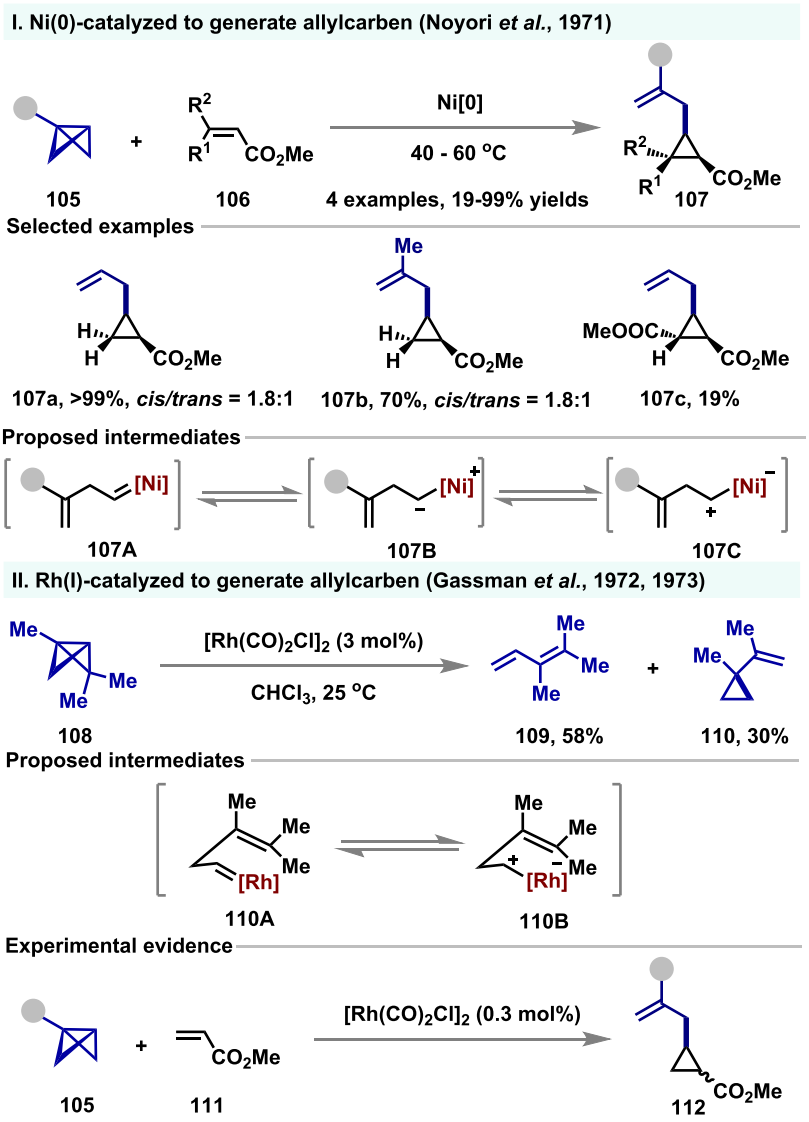
Scheme 35. Pioneer Works of BCBs as Carbene Precursors



[*cd*]indene scaffolds—with their rigid, three-dimensional architecture and multiple reactive sites—represent promising precursors for designing three-dimensional bioisosteres in drug discovery.

In 2021, the Glorius group achieved a three-component reaction between BCBs **105**, oxime ethers **124**, and aldehydes **125** using a Rh(III) catalyst, constructing sterically tertiary alcohol esters **126** with high stereoselectivity (Scheme 38).[131] The transformation exhibits excellent functional group tolerance, accommodating sensitive groups such as hydroxyls as well as heterocyclic moieties including thiophene (**126a**–**126c**). Mechanistic studies outline a plausible catalytic cycle. Initially, the Rh(III) precatalyst undergoes ligand exchange with cesium acetate (CsOAc) to generate the active Rh(III) species **126A**. Subsequent coordination and C−H activation of the oxime ether substrate affords rhodacyclic intermediate **126B**. BCB **105** then coordinates to the metal center and inserts into the Rh−C bond, forming Rh-cyclobutyl species **126C**. This intermediate undergoes β-carbon elimination to give **126D**, followed by *cis* β-hydride elimination/reinsertion to deliver π allyl species **126F** *via* key intermediate **126E**. Isomerization to a σ-allyl intermediate followed by addition to aldehyde **125** proceeds *via* a chair like six membered transition state **126G**, enabling precise control over product stereochemistry. Finally, protodemetalation releases the corresponding product **126** and regenerates the catalyst. Step control experiments failed to afford the product *via* a stepwise olefination aldol pathway, supporting a concerted reaction mechanism rather than a sequential process. In 2024, Zhang and co-workers employed density functional theory (DFT) calculations to provide further evidence that intermediate **126B** facilitates the release of ring strain in bicyclobutanes. This triggers a concerted cleavage of both the central carbon−carbon bridge bond and the two flanking C−C bonds, ultimately generating a rhodium carbene species **126B′**. This rhodium carbene is identified as a key intermediate that participates in and drives the ensuing transformation processes.[132]

4. STRAIN-RELEASE RING OPENING OF [1.1.1]PROPELLANE TO GENERATE CYCLOBUTYLCARBENE

[1.1.1]Propellane (TCP), a propeller shaped, highly strained cage molecule, can be viewed as three fused cyclopropane

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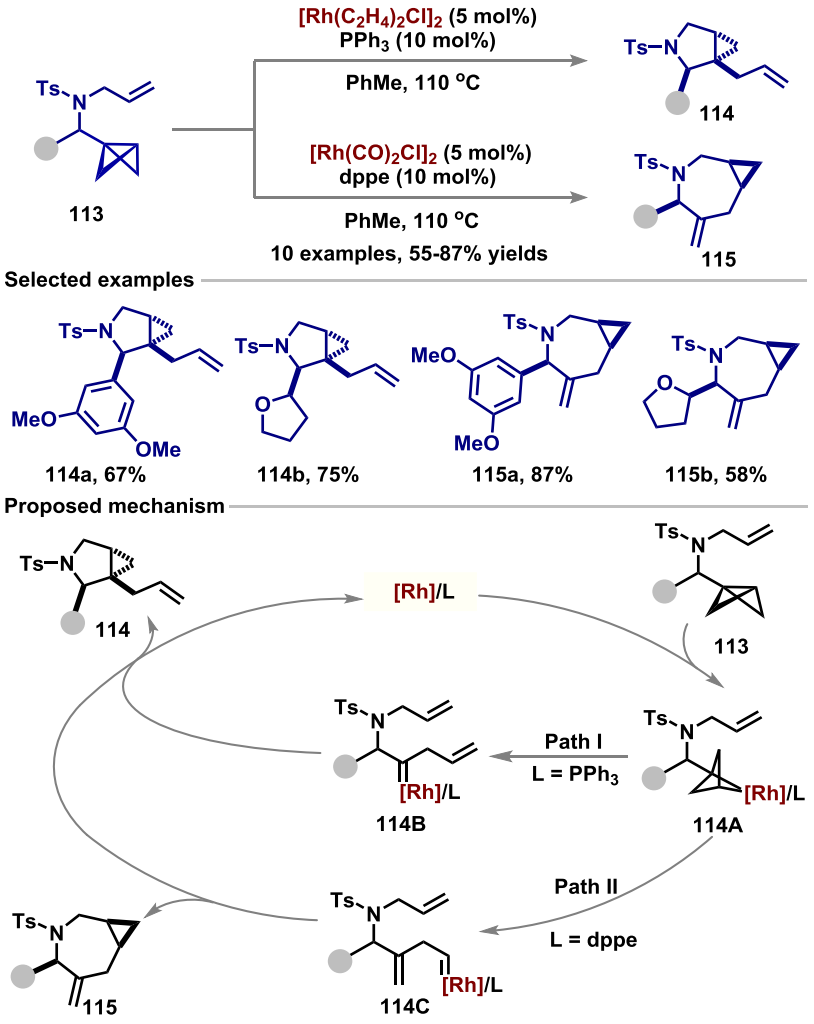
Scheme 36. Ligand-Controlled Selective Cyclopropanation of BCBs



rings sharing a central C−C bond.[133] With a ring strain of 98−113 kcal/mol—significantly exceeding the sum of three isolated cyclopropanes—the strain is concentrated in the unique central σ bond between the bridgehead carbons, imparting kinetic instability and distinct reactivity.[134] Due to its unconventional bonding and high strain, TCP was once considered a "non-existent" molecule.[135] In 1982, based on theoretical predictions, Wiberg and co-workers proposed that 1,3-disubstituted bicyclo[1.1.1]pentanes (BCPs) could form stable TCP structures and first successfully synthesized the compound.[136] A practical gram scale synthesis was later established by Szeimies and co-workers *via* a sequence involving dibromocyclopropanation of 3-chloro-2-chloromethylpropene, halogen−lithium exchange, and intramolecular nucleophilic substitution, rendering TCP readily accessible for systematic study.[137] The growing interest in BCPs as benzene bioisosteres in medicinal chemistry has further highlighted TCP as a strategic precursor to BCP scaffolds.[138] The strained central C−C bond readily undergoes ring opening bifunctionalization upon attack by radicals or nucleophiles, enabling diverse routes to *para* disubstituted BCP analogues.[139]

Notably, under thermolysis (high temperature) or transition metal catalysis, TCP releases strain through cleavage of the central C−C bond and isomerizes to a cyclobutylcarbene intermediate—a carbene precursor that is otherwise challenging to access.[140] In 1986, Szeimies and colleagues observed that thermolysis of TCP at 430 °C in a flow system afforded diene substituted cyclopropane **128** as the main product (Scheme 39, **I**).[141] Subsequent computational studies by Pierini et al. using the PRDDO-RHF method identified cyclobutylcarbene **128A** as a key intermediate.[142] Wiberg and co-workers subsequently demonstrated that transition metals can mediate TCP ring opening to cyclobutylcarbenes, with product selectivity heavily dependent on the metal and its oxidation state (Scheme 39, **II**).[143] Rh(I) and Pd(II) catalysts rapidly afforded dimer **129** and methylenecyclobutene **130**, whereas Ag(I), Ir(I), Pt(II), and Pt(0) systems showed lower selectivity and slower rates. Trapping experiments with methyl acrylate **131** generated cyclopropane **132** together with dimer **129**, providing direct evidence for carbene intermediate. Although these early studies revealed the high reactivity and synthetic potential of TCP as a carbene precursor under transition metal catalysis, the field remained underexplored for an extended period.

Recently, with advances in transition metal catalysis and a renewed focus on strained scaffolds, TCP has re emerged as a valuable carbene source. The cyclobutylcarbene intermediate generated from TCP incorporates both an olefin unit and a cyclobutane framework. The latter, with its rigid conformation and high C(sp^3) content, not only serves as a bioisostere of aromatic rings but also appears as a key structural motif

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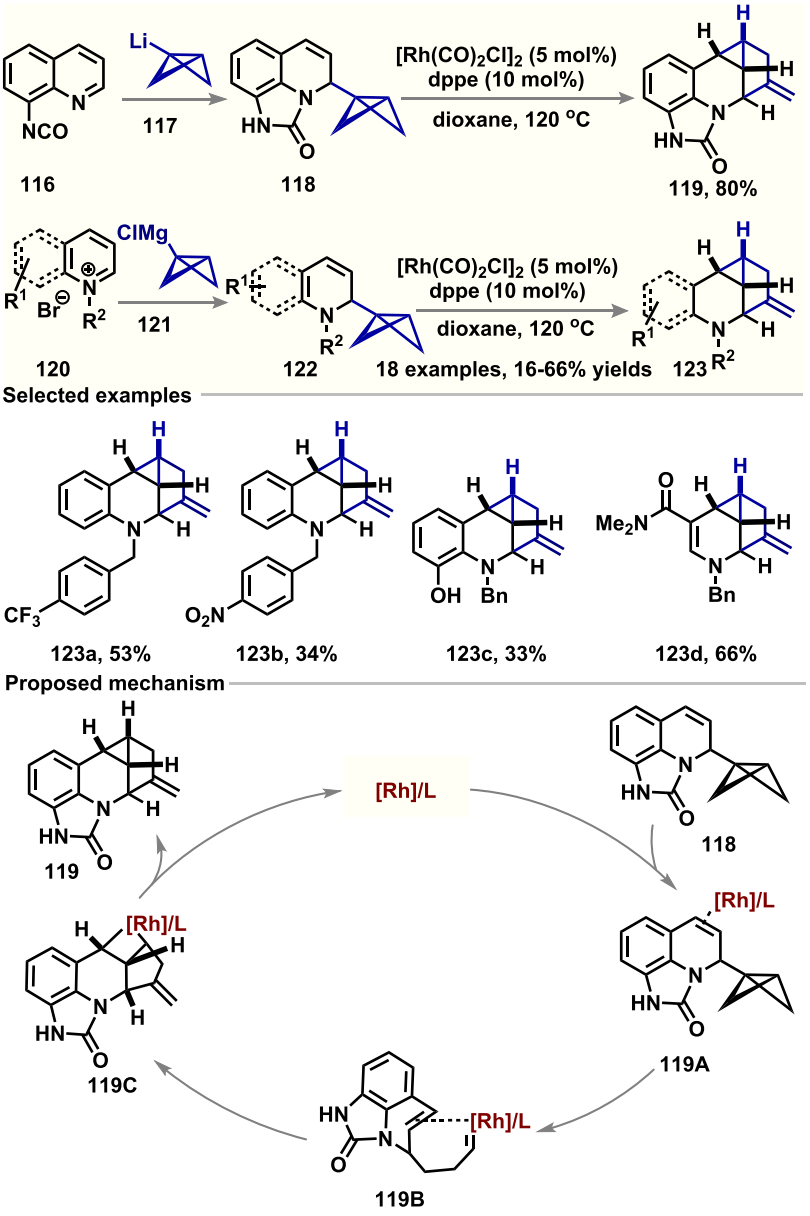
Scheme 37. Rh-Catalyzed Annulation of BCBs with Dihydroquinolines and Dihydropyridines



constructing complex cyclobutane skeletons in total synthesis.[144] The following section highlights recent progress in employing TCP as a carbene precursor for the synthesis of substituted cyclobutanes.

Early studies relied on the cyclopropanation of TCP with electron deficient alkenes under rhodium catalysis as direct evidence for carbene intermediate formation. However, these reactions predominantly generated dimeric by products and lacked practical synthetic utility. Furthermore, the inherent instability of the resulting cyclobutylcarbene intermediates—prone to insertion and rearrangement—impeded detailed mechanistic study for decades. In 2019, the Aggarwal group reported a nickel catalyzed cyclopropanation of TCP with various functionalized alkenes **13**, constructing unique small ring of spirocyclic scaffolds **133** (Scheme 40).[145] Catalyst screening revealed that transition metals such as Rh(I), Ir(I), Pd(0), and Cu(I) failed to effectively suppress the dimerization of TCP, while Ni(0) complexes exhibited superior catalytic performance and chemoselectivity. The reaction displays broad substrate scope (Scheme 40, I): styrene derivatives bearing electron withdrawing groups (esters, cyano) reacted smoothly (**133a**−**133b**); heteroaromatic alkenes such as pyridines and indoles also showed excellent reactivity (**133c**−**133d**); conjugated dienes participated efficiently at room temperature with high regioselectivity, where the carbene selectively underwent cyclopropanation with the terminal alkene to afford **133e**. Furthermore, vinyl boronate **134** was similarly transformed into the quaternary cyclopropylboronate **135** under analogous conditions (Scheme 40, II). Isotope labeling experiments and DFT calculations support a stereospecific nickel carbene pathway rather than a radical mechanism. The proposed catalytic cycle commences with the *in situ* generation of an active Ni(0)−NHC species from $Ni(cod)_2$ and SIMes, itself formed from 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (SIMes·HCl) and sodium *tert*-butoxide (^{t}BuONa). This species coordinates two alkene molecules, one of which subsequently dissociates to furnish intermediate **133A**.

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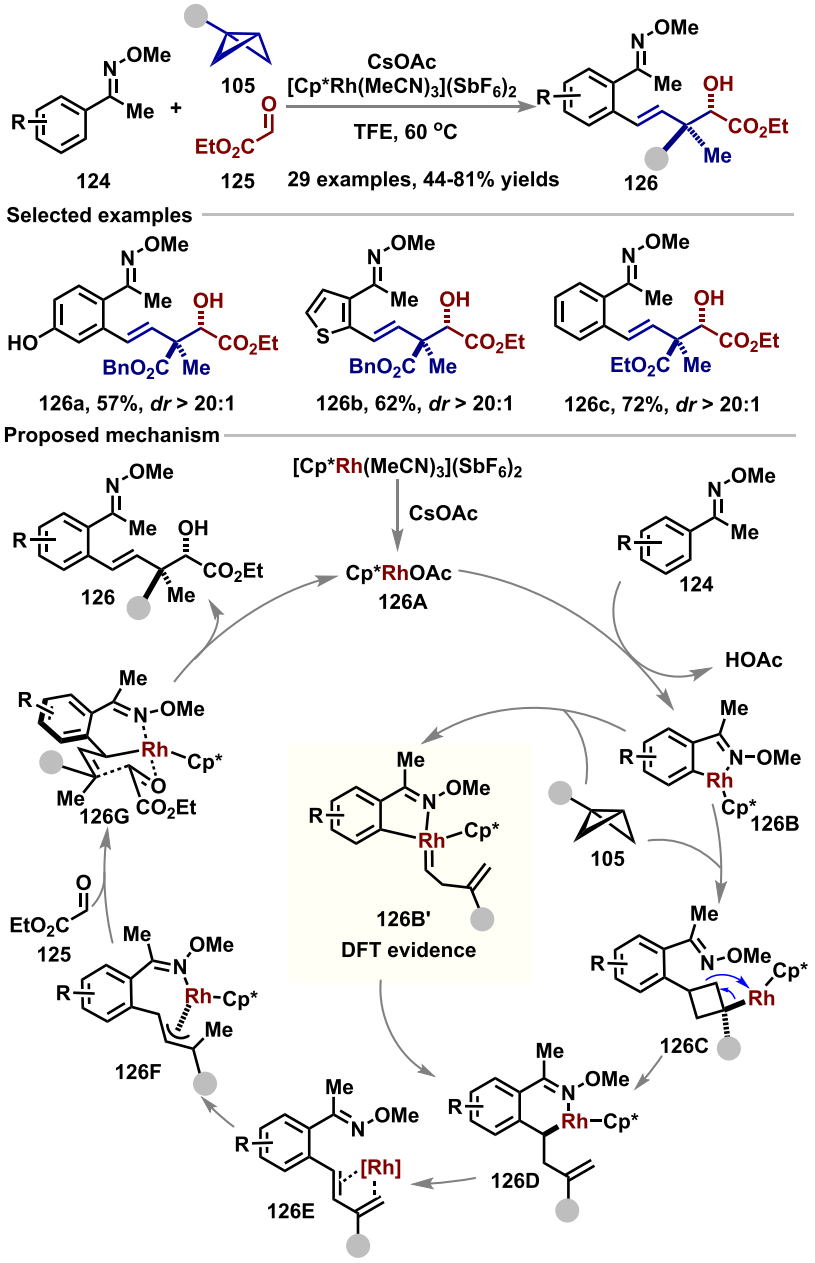
Scheme 38. Rh(III)-Catalyzed Strain-Release of BCBs to Construct of Quaternary Carbon Centers



Coordination of TCP **127** then affords adduct **133B**, which undergoes a concerted cleavage of two C−C bonds—the central bridge and one peripheral cyclopropane bond—*via* intermediate **133C**. This ring-opening event delivers the key cyclobutyl− nickel carbene intermediate **133D**. Subsequent insertion of the carbene into the alkene proceeds through a metallacyclobutane transition state **133E**, followed by reductive elimination to generate nickel complex **133F** *via* transition state **133-TS**. Finally, reaction of **133F** with another equivalent of alkene releases the cyclopropane product and regenerates the catalyst. This study overcame the long-standing limitation of polymerization side reactions in transition metal catalyzed TCP transformations, opening a new avenue for constructing complex molecules containing cyclobutane units.

Traditional diazo and hydrazone carbene precursors are widely used for allene synthesis,[146] yet the construction of exocyclic allene substituted cyclobutanes has been hindered by the difficulty of accessing cyclobutylcarbene precursors. In 2019, Tolnai and co-workers developed a copper catalyzed ring opening/coupling of TCP with terminal alkynes, providing divergent access to either cyclobutane framed allenes **137** or alkynyl substituted cyclobutanes **138** (Scheme 41).[147] The reaction proceeds *via* a copper promoted TCP ring opening to a cyclobutyl copper complex. Evaluating of temperature, solvent, and ligands enables selective coupling with alkynes, delivering either allene or alkyne products. The method demonstrates good tolerance toward sensitive functional groups, accommodating substrates bearing bromo **137a**, formyl **137b**, and amino **137c** substituents. Notably, silyl substituted alkynes selectively furnish cyclobutylalkynes **138**, likely due to enhanced nucleophilicity of the copper intermediate imparted by the silyl group's electron donating and steric properties. Two plausible pathways are proposed:

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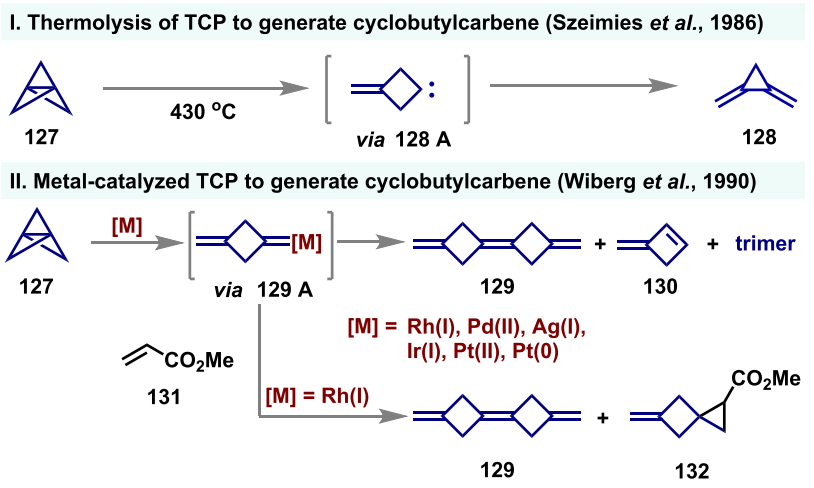
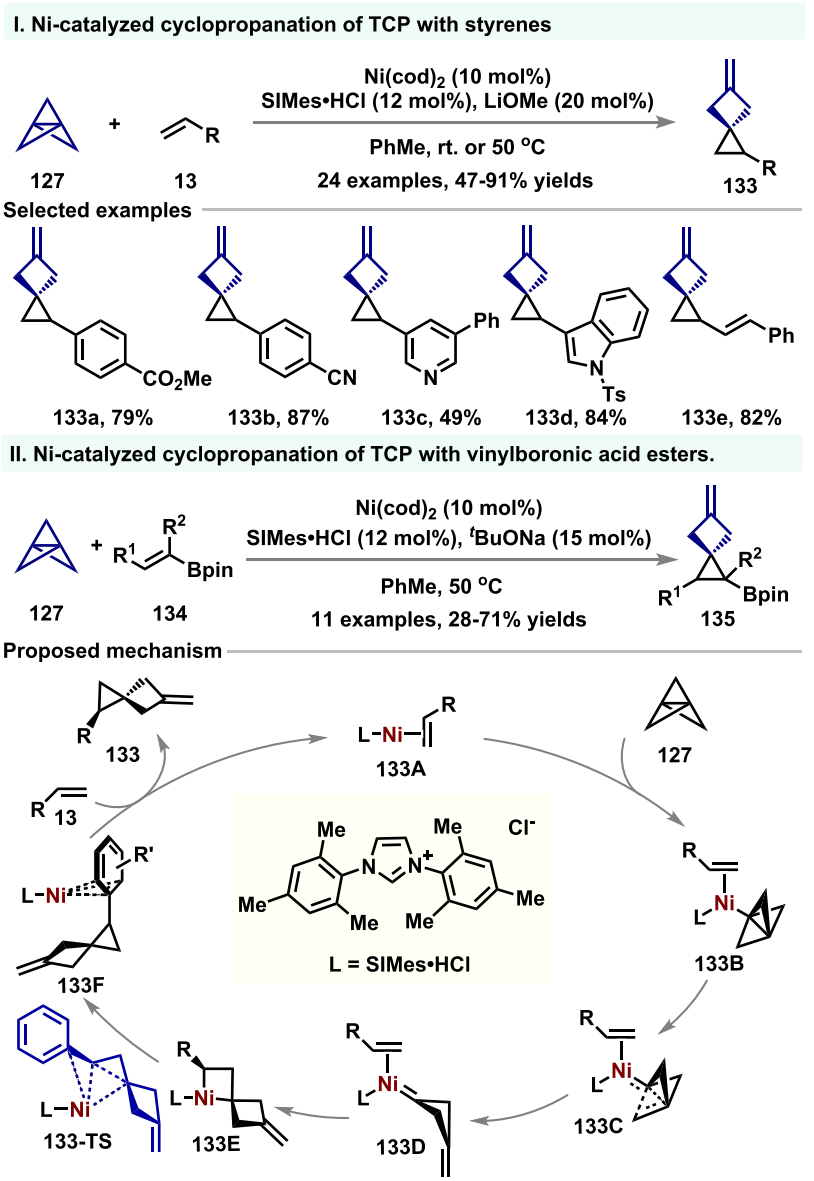
Scheme 39. Pioneer Works of TCP as Carbene Precursors



Scheme 40. Ni-Catalyzed Cyclopropanation of TCP as Carbene Precursors



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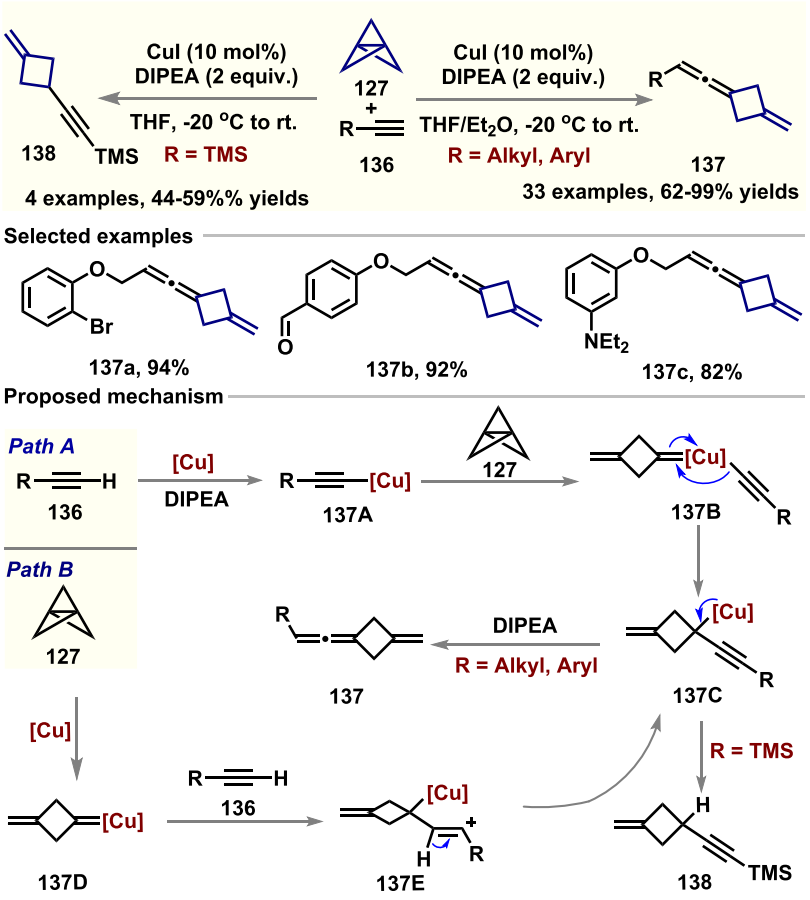
Scheme 41. Cu-Catalyzed Ring-Opening of TCP with Alkynes



path A: Cu(I) coordination to the alkyne gives **137A**, which reacts with TCP to form copper carbene **137B**, followed by migratory insertion to **137C**; or path B: initial TCP coordination affords copper carbene **137D**, which is attacked by the alkyne to afford **137C** after deprotonation. The outcome then diverges: alkyl/aryl alkynes undergo copper migration followed by protodemetalation *via* **137C** to give allene **137**, whereas silyl alkynes undergo direct protonation to furnish alkyne **138**. This work clarifies the versatile reactivity of cyclobutylcarbenes in alkyne functionalization and offers a practical strategy for accessing cyclobutylallene scaffolds.

In multicomponent carbene reactions, carbenes typically react with nucleophiles to form key ylide intermediates, which then undergo further transformation with a third component.[148] Cyclobutylcarbenes generated from TCP can also engage in such pathways. In 2023, Hong and co-workers developed a silver catalyzed three component reaction using TCP as a cyclobutylcarbene precursor to construct methylenecyclobutanes (Scheme 42).[149] Employing silver hexafluoroantimonate ($AgSbF_6$) as a weakly coordinating anion catalyst, the strained TCP framework is selectively activated. The Ag(I) center modulates the carbene reactivity, suppressing dimerization and decomposition. The resulting silver carbene intermediate reacts with cyclic ethers (e.g., tetrahydrofuran, dioxane) to form an ylide type species, which then couples with nucleophiles such as anilines or alcohols to deliver methylenecyclobutanes **141**. The reaction proceeds under mild conditions with broad substrate scope. Anilines bearing electron donating, electron withdrawing, or heterocyclic substituents react efficiently (**141a**−**141c**). Various cyclic ethers undergo selective ring opening (**141d**−**141e**), and the method is applicable to late-stage modification of bioactive molecules including cholesterol derivative **141f** and aminoglutethimide **141g**. A plausible reaction pathway is proposed. TCP coordinates with Ag(I) to form **141A**, which undergoes central C−C bond cleavage to generate the reactive silver methylenecyclobutyl carbenoid **141B**. Subsequent regioselective nucleophilic attack by the cyclic ether oxygen affords the key silver oxonium ylide **141C**. Finally, C−O bond cleavage and proton transfer mediated by nucleophile **140** release the product **141** and regenerate the catalyst. This strategy overcomes common polymerization side reactions of cyclobutylcarbenes and provides a controlled route to diverse cyclobutane scaffolds.

Building on previous silver catalyzed carbene transfer from TCP, in 2024, the Hong group developed an iron catalyzed three component difunctionalization of TCP (Scheme 43).[150] In contrast to earlier linear methylenecyclobutane formations, this strategy simultaneously opens the TCP ring and installs two functional groups at its 1,3-positions, delivering non-linear, polysubstituted cyclobutanes **143** with quaternary stereocenters. The reaction is enabled by *in situ* generation of an acidic species from *N*-amidopyridinium salt **142** and an alcohol, which protonates TCP to trigger ring-strain driven ring opening and formation of a cyclobutyl−iron carbeniod. The mild catalytic system tolerates various alcohols and pyridinium salts (**143a**−**143d**) and allows late-stage functionalization of pyridine containing bioactive molecules such as Vismodegib **143e** and Pyriproxyfen **143f**. This TCP

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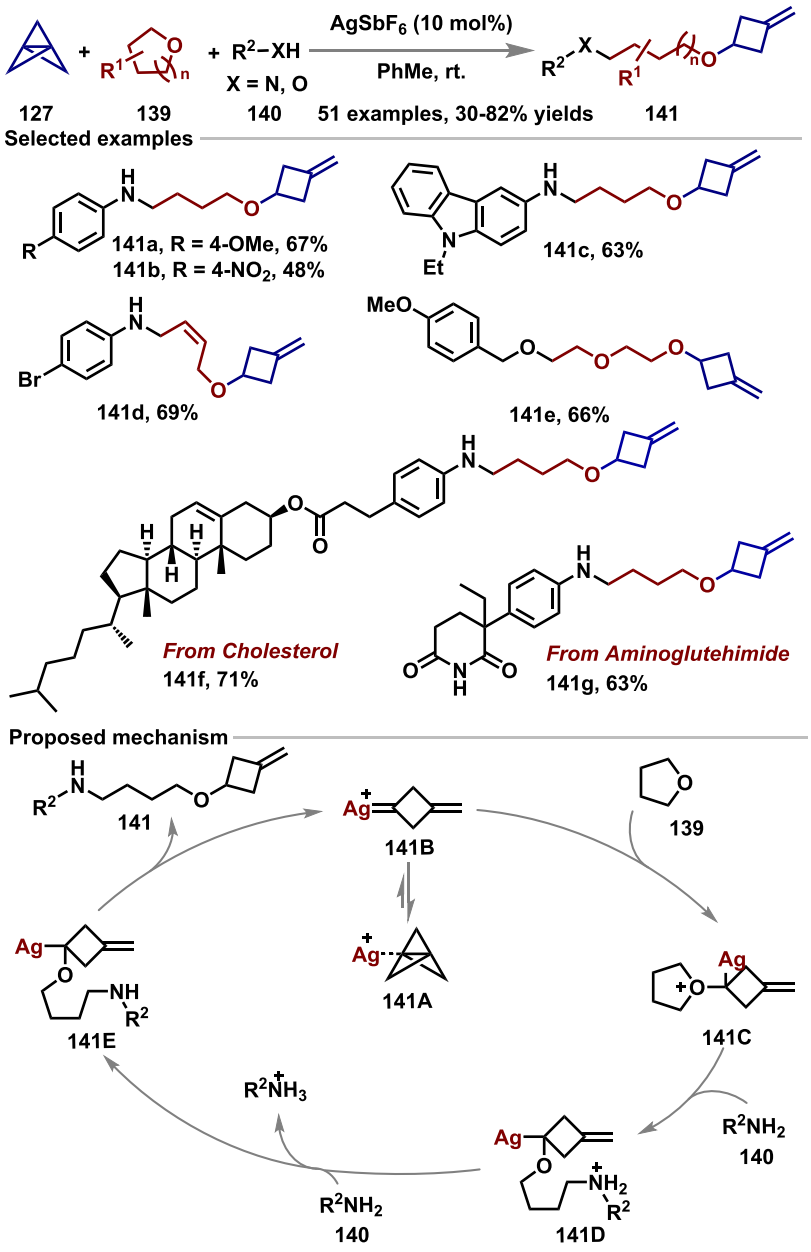
Scheme 42. Ag-Catalyzed Multiple-Component Reactions with TCP



difunctionalization concurrently establishes two carbon stereocenters, including an internal quaternary center bearing methyl and pyridyl groups, providing a valuable scaffold for future asymmetric catalysis. Mechanistically, nucleophilic attack of the alcohol on the *N*-acylpyridinium salt **142** generates the key oxonium ion **143A**. Protonation of TCP then triggers its rearrangement to afford the cationic intermediate **143C**. Subsequent alcohol addition converts this cation into the methylenecyclobutane **143E** *via* **143D**. Notably, in the absence of the *N*-amidopyridinium salt, a certain amount of **143E** can also be formed under iron catalysis, suggesting that an iron carbenoid complex **143F** may operate as a plausible competing pathway. In the iron-catalyzed cycle, FeX_3(III) undergoes alcoholysis to generate the activated species **143J**, which subsequently engages in hydride/alkoxy exchange with the silane to form the key iron hydride **143 K**. This hydride reacts with the alkene *via* a Metal−Hydrogen Atom Transfer (MHAT) process to produce a Markovnikov-type alkyl radical **143G**, which then undergoes radical addition to the *N*-acylpyridinium salt **142** at the C4 position. Deprotonation affords the target product **143**, while the concomitantly generated radical **143H** serves as an endogenous oxidant to complete regeneration of the iron catalyst.

Fluorine chemistry is pivotal in drug discovery, and strained aliphatic small rings serve as valuable bioisosteres.[151] The construction of fluorinated small ring systems is therefore highly desirable.[152] In 2024, the Zhang group reported a copper catalyzed three component reaction of TCP that simultaneously cleaves two C−C bonds and forms two new ones, delivering nonlinear gem difluoroallylated cyclobutanes with quaternary centers (Scheme 44).[153] Using their own developed electrophilic 3,3-difluoroallyl sulfonium salts (DFAS) as a fluoroalkylating reagent and organozinc reagents **144** as nucleophiles,[154] the reaction proceeds under copper catalysis with TCP as the carbene precursor. The

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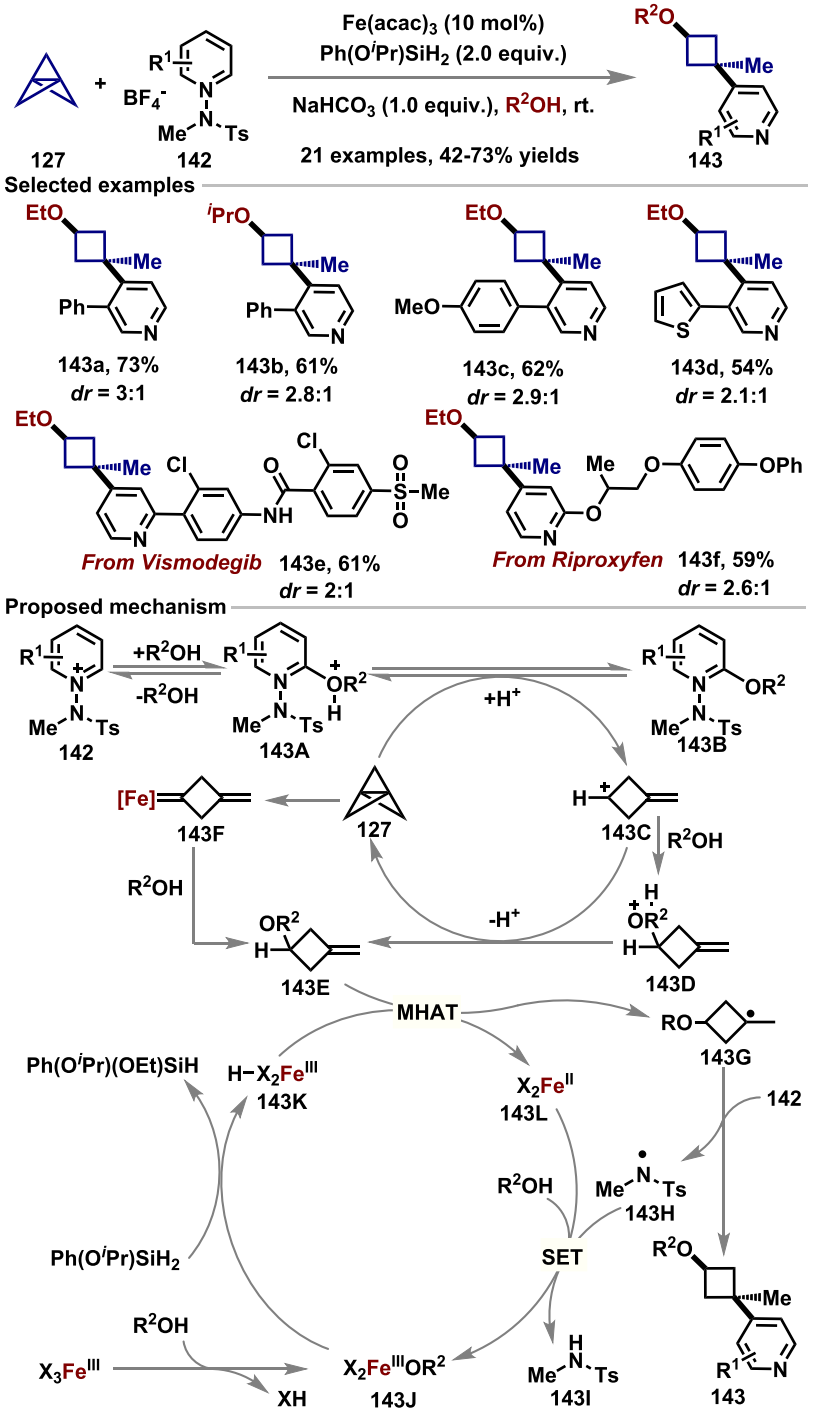
Scheme 43. Fe-Catalyzed 1,3-Difunctionalization of TCP



system tolerates diverse substrates, including aromatic zinc reagents with electron donating **145a** or electron withdrawing **145b** groups, alkyl Grignard reagents, allylzinc species, and α brominated DFAS **145c**. Notably, *para* ester or cyano substituted arylzinc reagents generate products **146a** or **146b** that feature a direct BCP-cyclobutane linkage—a hybrid scaffold merging two important bioactive ring systems. Carbohydrate derived reagents also participate effectively **146c**. A plausible mechanism involves two pathways. In path A, Cu(I) coordinates TCP to form copper carbene **145A**, which undergoes transmetalation to give cyclobutyl copper **145B**. Oxidative addition of DFAS yields Cu(III) intermediate **145C**, and reductive elimination delivers product **145** while regenerating Cu(I). Path B proposes initial formation of Cu organometallic species **145D** from the zinc reagent, followed by TCP insertion to form carbene **145E** and then **145B**. Alternatively, **145B** can react with a second TCP to form BCP copper species **145F**, which couples with DFAS to afford the linked BCP−cyclobutane product **146**. This work overcomes limitations of traditional fluoroalkylation by employing DFAS as a highly electrophilic reagent.

The Doyle Kirmse reaction represents a classical [2,3]-sigmatropic rearrangement in organic synthesis. It was

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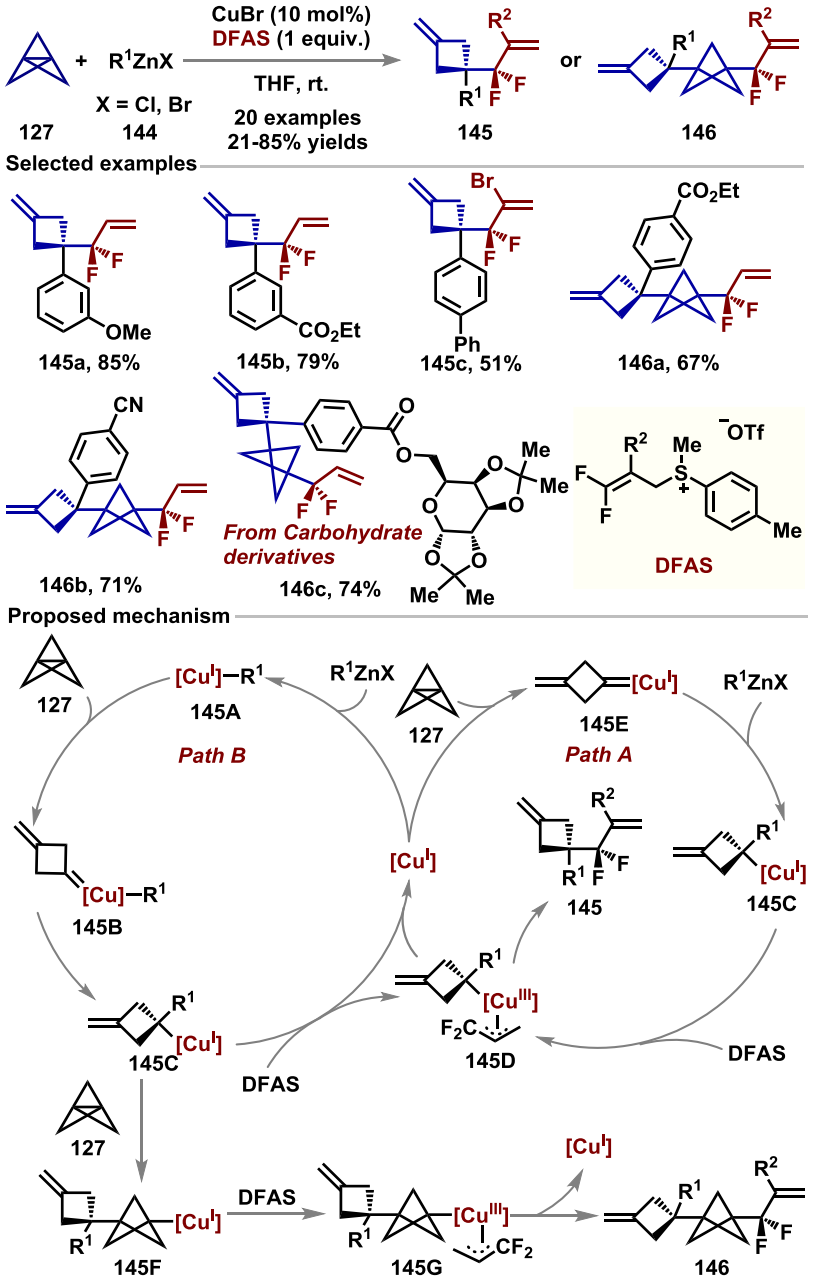
Scheme 44. Cu-Catalyzed Synthesis of *gem*-Difluoroallylated Cyclobutanes



initially reported by W. Kirmse in 1968 and subsequently refined by M. P. Doyle in 1981.[155] Typically conducted under transition metal catalysis, the reaction employs α-diazo esters or hydrazones as carbene precursors that react with allylic or propargylic thio or selenoethers. The metal carbene intermediate coordinates with the sulfur or selenium atom to generate the corresponding ylide, which then undergoes a [2,3]-sigmatropic rearrangement to form new C−C and C−S/Se bonds, thereby reorganizing the molecular framework. Recently, the Hari group reported a metal catalyzed Doyle Kirmse reaction involving TCP (Scheme 45).[156] Through copper catalyzed dual C−C bond activation, a cyclobutyl−copper carbene intermediate is generated, driving the [2,3]-sigmatropic rearrangement to efficiently deliver a series of allenylated or allylated methylenecyclobutane derivatives. The catalytic system exhibits broad substrate generality, accommodating both electron donating and electron withdrawing aryl propargyl thioethers with good functional group tolerance **148a**. Internal alkynes are also compatible, with phenyl substituted variants furnishing gem disubstituted allene **148b**. Phenyl propargyl selenoethers perform similarly **148c**, and the strategy extends efficiently to thioethers or selenoethers, delivering allylated products (**150a**−**150d**). DFT calculations suggest that copper activates TCP *via* cleavage of the central and one peripheral C−C bond, generating cyclobutyl−copper carbene **150B**. This complex reacts with the thioether to form copper coordinated ylide **150C**, which undergoes [2,3]-sigmatropic rearrangement through a copper participating five membered transition state **150D**, releasing the catalyst and affording product **150**. This work highlights the distinct reactivity of highly strained small ring molecules in carbene chemistry and their utility for constructing functionalized cyclobutane scaffolds.

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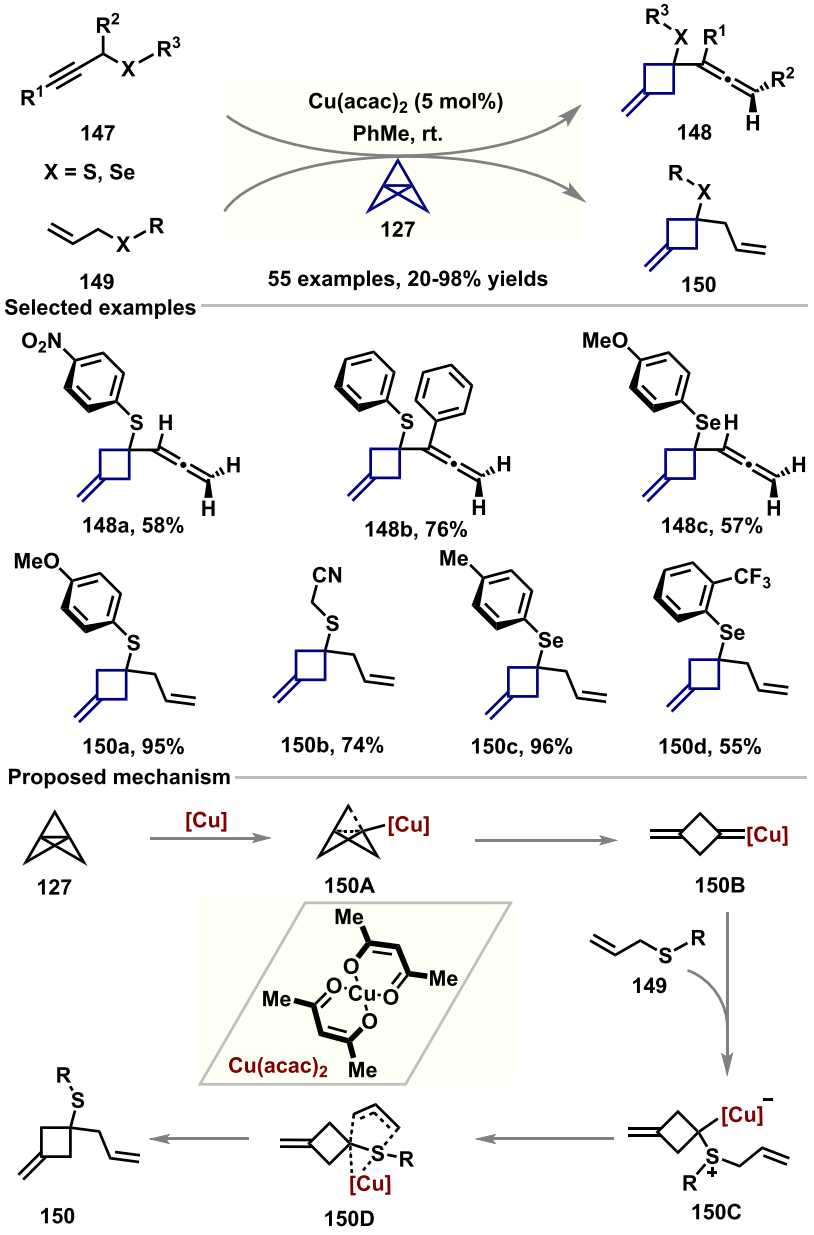
Scheme 45. Cu-Catalyzed Doyle-Kirmse Reactions with TCP



Recently, Luo et al. developed a copper-catalyzed, diastereoselective addition of TCP to *N-tert*-butylsulfinyl imines, providing direct access to bismethylenecyclobutane dimers bearing two chiral centers. These cyclobutane-rich scaffolds serve as potential biphenyl bioisosteres (Scheme 46).[157] The reaction proceeds *via* copper-mediated TCP ring-opening to a carbene intermediate **152A**, which dimerizes to form a nucleophilic bicyclobutane **152B**. Subsequent interception by the sulfinyl imine **151**, acting as an electrophile and stereodirecting ligand, delivers the product **152** with good stereoselectivity. This reaction system exhibits broad compatibility with various sulfinyl imine substrates. Substrates bearing strong electron-donating groups such as methoxy showed slightly lower yield and diastereomeric ratio **152a**. In contrast, electron-withdrawing substituents including ester and trifluoromethyl groups maintained both high reactivity and diastereoselectivity (**152b**−**152c**). Heterocycle-substituted substrates also demonstrated high reactivity (**152d**−**152f**). Notably, *N*-containing heterocycles such as pyridine led to a decreased *dr* value **152f**, likely due to competitive coordination of the nitrogen atom with the copper catalyst. Furthermore, *α*-aliphatic substituted imine substrates **152g** reacted smoothly under the standard conditions with moderate yield and excellent diastereoselectivity. Derivatives containing complex bioactive motifs **152h** remained stable under the mild reaction conditions and were successfully transformed.

5. STRAIN-RELEASE RING OPENING OF OTHER SMALL-RING SYSTEMS TO GENERATE CARBENE

Methylenecyclopropanes (MCPs), which integrate a strained cyclopropane ring with an exocyclic alkene unit, have attracted significant interest owing to their easy synthetic accessibility and multiple reactive sites.[158] The inherent ring strain of cyclopropane (~40.9 kcal/mol) combined with the olefinic character of the exocyclic double bond enables MCPs

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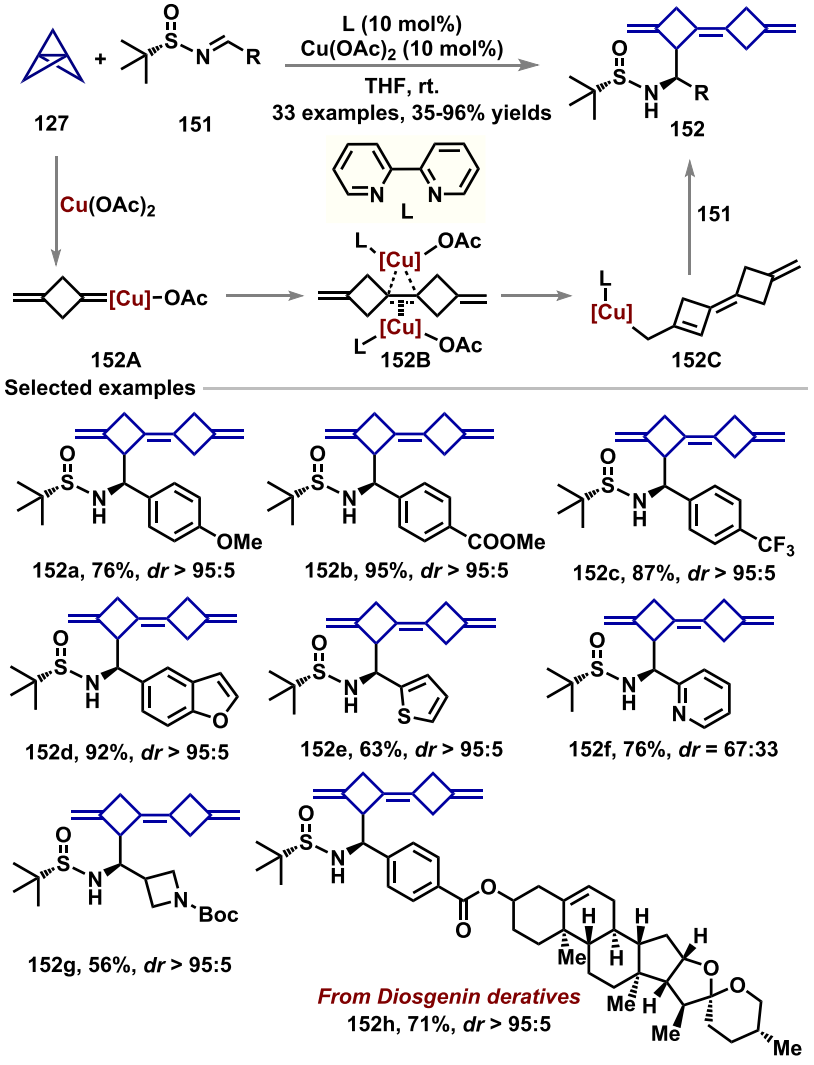
Scheme 46. Cu-Catalyzed Diastereoselective Addition of TCP Dimer to Imines



to undergo diverse ring opening transformations under transition metal catalysis, establishing them as versatile C_4 synthons.[159] Particularly noteworthy is the activation of the C═C bond of MCPs by soft Lewis acidic metal cations such as Pt(II), Au(I), and Au(III), which can trigger strain driven isomerization to form metal stabilized carbene complexes. In 2006, the Fürstner group demonstrated that coordination of Pt^{2+} to the double bond of MCPs **153** induces cyclopropane ring expansion **154A**, generating a cyclobutylcarbene species **154B** that leads to cyclobutene derivatives **154** *via* cyclobutyl-Pt complex **154C** (Scheme 47, **I**).[160] The addition of CO gas to the reaction system further accelerates the transformation and improves yields, presumably *via* enhanced metal ligand coordination. This process exhibits broad substrate generality, tolerating both aliphatic and aromatic substituents on the alkene as well as electron donating or electron withdrawing groups on the arene ring (**154a**−**154d**). Concurrently, the Shi group reported a Pd-catalyzed isomerization/ring expansion of MCPs **153** to afford cyclobutene **154** (Scheme 47, **II**).[161] A plausible mechanistic pathway begins with the addition of palladium bromide ($PdBr_2$) across the alkene to form intermediate **154B**, followed by β-hydride elimination to give π-allylpalladium species **154C**. Subsequent regioselective reverse hydropalladation affords complex **154D**, which undergoes α-bromide migration to generate the key palladium carbene intermediate **154E**. Cycloisomerization of **154E** then delivers cyclobutene **154** while regenerating the $PdBr_2$ catalyst.

In 2014, the Echavarren group developed a gold(I)-catalyzed formal [4 + 1] cyclization between MCPs **153** and cycloheptatriene **155** (Scheme 48).[162] In this tandem cyclization, the gold(I) catalyst plays a critical dual role. It promotes the ring expansion of MCP **153** *via* a cyclobutyl−gold carbene complex **156A**, which isomerizes to cyclobutene **156B** acting as a C_4 synthon, while simultaneously activating cycloheptatriene **155** through a retro Büchner reaction to generate a gold carbene species **156C**. Ultimately, the two intermediates engage in a cyclopropanation/ring opening cascade to afford the cyclopentene product **156**. MCPs and cycloheptatrienes bearing either electron donating or electron withdrawing substituents on the aryl rings undergo smooth transformation (**156a**−**156c**). However, *ortho*-substitution on the aryl ring of the MCP significantly reduces the yield **156d**. Mechanistically, Cyclopropanation of cyclobutene **156B** by carbenoid **156C** then generates housane intermediate **156D**. Subsequent gold(I)-catalyzed cleavage of a bridge C−C bond in **156D** gives tertiary carbocation **156E**, which undergoes a 1,2-hydride shift to furnish the final cyclopentene product

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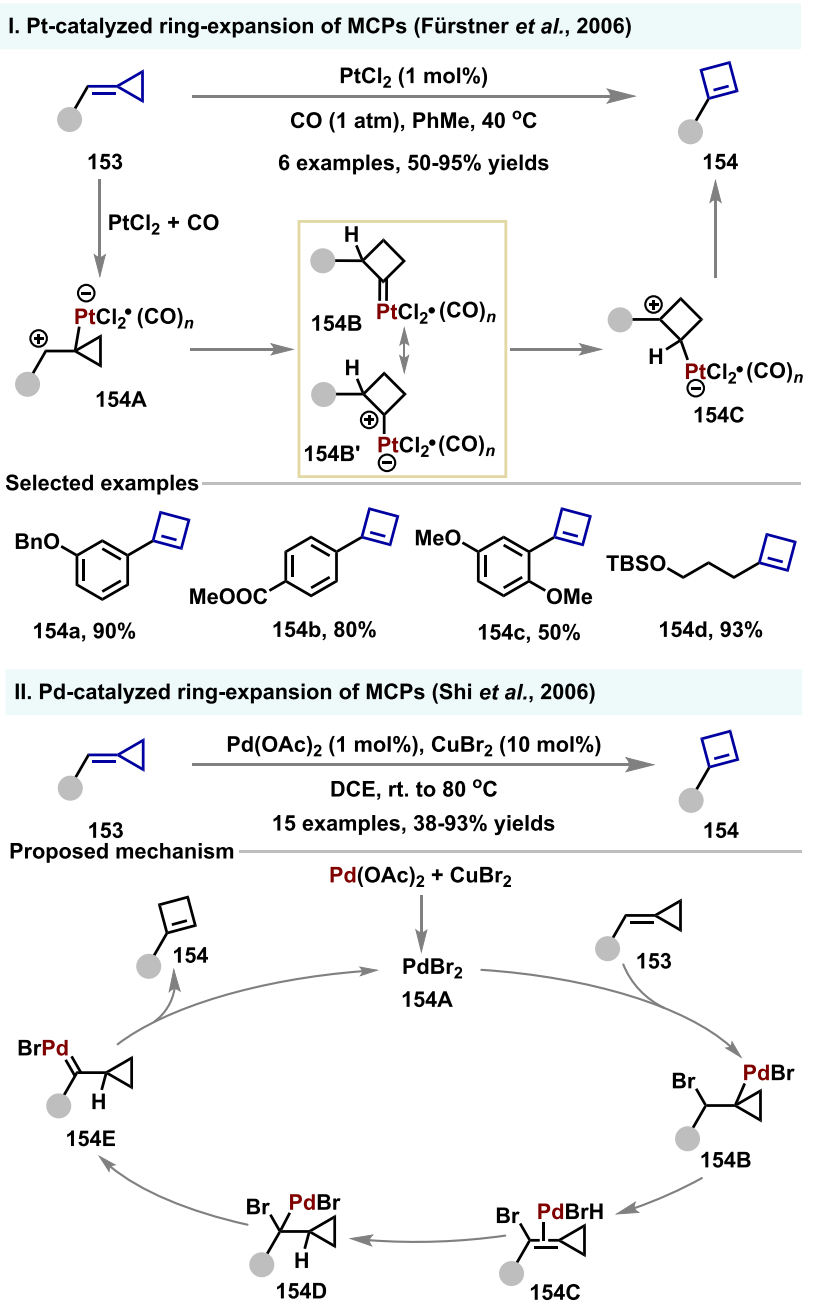
Scheme 47. Pioneer Works of MCPs as Carbene Precursors



156. This transformation highlights the unique reactivity of MCPs in cascade carbene processes.

The Shi group later applied MCP-involved cascade reactions to construct oxygen and nitrogen containing heterocycles bearing cyclobutene motifs. In 2016, they designed an *ortho* propargyl ether substituted MCPs **157** and achieved a gold catalyzed one pot cascade toward cyclobutenyl 2*H*-chromene derivatives (Scheme 49).[163] MCP bearing methyl or halogen substituents on the benzene ring were compatible with the reaction, affording the corresponding products (**158a**−**158c**). Introduction of a methyl group at the *para* position, acting as an electron-donating substituent, increased the electron density at the *meta* position. When a phenyl group was introduced at the terminal alkyne, the desired product **158d** was obtained in 76% yield. Mechanistically, 1,3-bis(2,6-diisopropylphenyl)-imidazole ($IPrAuSbF_6$) activates the alkyne to form **158A**/**158A′**, which undergoes hydroarylation to give gold complex **158B**. Protonolysis releases the gold catalyst and genertates **158C**. Re entry of the gold catalyst activates the MCP, generating a reactive gold cation that rearranges to carbene **158D**; a final 1,2-hydride shift delivers product **158**.

In a later study, an *ortho*-amino substituted MCP substrate **159** was designed and transformed under gold catalysis into 1,2-dihydroquinoline derivatives **160** containing a cyclobutene unit (Scheme 50).[164] Both electron-donating and electron-withdrawing substituents introduced on the two aromatic rings of MCP were well tolerated and afforded the desired products (**160a**−**160b**). However, heterocyclic substrates such as thiophene-substituted derivatives afforded only trace amounts of a complex mixture **160c**. The bromide substitution could be compatible in this catalytic system

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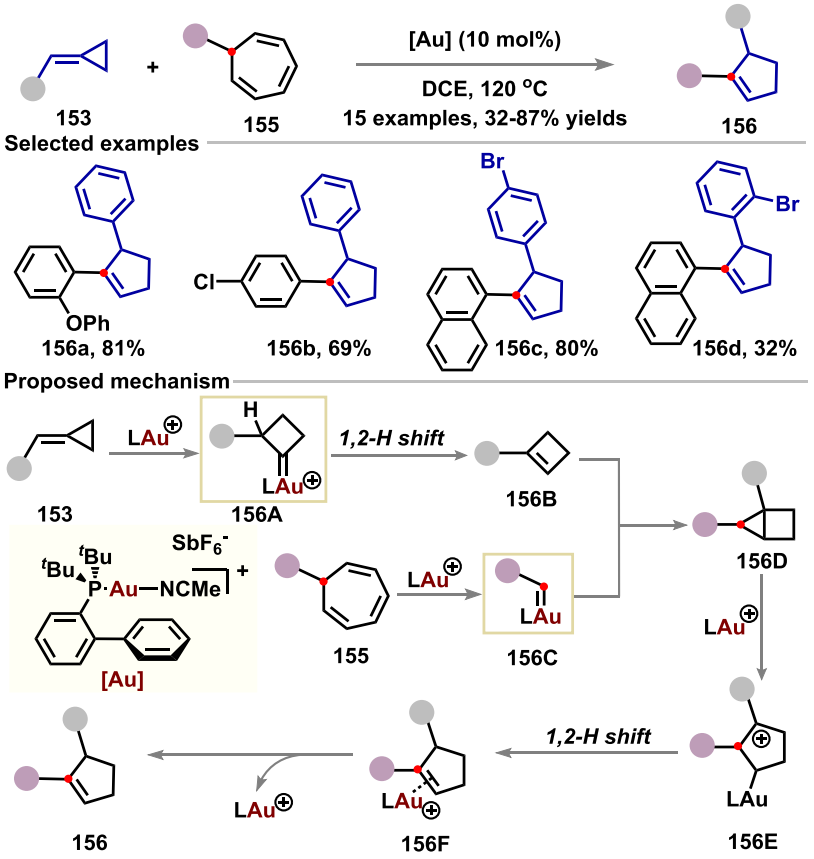
Scheme 48. Formal [4 + 1] Cyclization of MCPs with Cycloheptatrienes



160d. This transformation is initiated by the coordination and activation of the alkyne unit in **159** by the Au(I) catalyst, leading to the intermediate **160A**. It is followed by an enyne cyclization to generate the key carbene intermediate **160B**. Subsequently, this carbene specie undergoes an intramolecular rearrangement to afford intermediate **160C**. Then, **160C** undergoes C−C bond cleavage to generate the cyclopropyl gold carbene intermediate **160D**, which further undergoes a ring-expansion process to form intermediate **160E**. Finally, elimination of the gold catalyst delivers the cyclobutene-containing product **160**.

In 2018, the Shi group further extended MCP involved cascade reactions to construct spirocyclic compounds containing fluorene and 1,2-dihydronaphthalene frameworks (Scheme 51).[165] In this work, they designed a bromo substituted MCP substrate **161**, which undergoes an intramolecular Heck type carbopalladation in the presence of Pd(0) catalysis, followed by β-hydride elimination and further isomerization to generate cyclopropene intermediate **162A**. This intermediate was confirmed by characteristic signals in its ^{13}C NMR spectrum. Subsequently, the cyclopropene species further transforms into the key vinyl−palladium carbene intermediate **162B**, ultimately affording the spirocyclic product **162**. This sequence reveals a novel MCP ring opening/cascade cyclization pathway *via* a palladium carbene intermediate. The reaction demonstrates good compatibility with various aryl substituents; both electron donating and electron withdrawing groups have minimal impact on efficiency (**162a**−**162c**). However, substrates bearing heteroaromatic rings afforded only trace amounts of the target product **162d**, suggesting that heteroatoms may interfere with the reaction pathway. Notably, the method was successfully applied to the late-stage modification of D-δ-tocopherol **162e**, highlighting its potential for functionalizing complex bioactive molecules.

Vinylidenecyclopropanes (VDCPs)—structurally analogous to methylenecyclopropanes—feature an allene unit fused to a strained cyclopropane ring, with a ring strain of approximately 50.9 kcal/mol. Their high strain energy and distinctive topology have established VDCPs as versatile C_2, C_3, or C_4 synthons in synthetic chemistry.[17] The Shi group has systematically developed gold catalyzed transformations of VDCPs that proceed *via* carbene intermediates, enabling diverse reaction modes such as oxidative ring expansion, intramolecular cyclopropanation, C−O bond cleavage, and asymmetric C(sp^3)−H insertion. In 2012, they disclosed a gold(I) catalyzed oxidative ring expansion of VDCPs **163** with pyridine *N*-oxide **164** to afford cyclobutanones **165** (Scheme 52, **I**).[166] This work proposed—and supported with computational evidence—the formation of cyclobutyl−gold carbene intermediate **165C** through VDCP isomerization/ring expansion, which is then oxidized by **164** to give the cyclobutanone product. To further verify the existence and synthetic utility of the cyclobutylcarbene intermediate in VDCP reactions, the team designed and synthesized VDCP substrates **166** containing an internal alkene in 2015. These substrates underwent gold catalyzed intramolecular cyclopropanation to furnish cyclopropane products (Scheme 52, **II**).[167] The successful implementation of this cyclopropanation reaction provided direct experimental evidence for the generation of a gold carbene intermediate from VDCPs.

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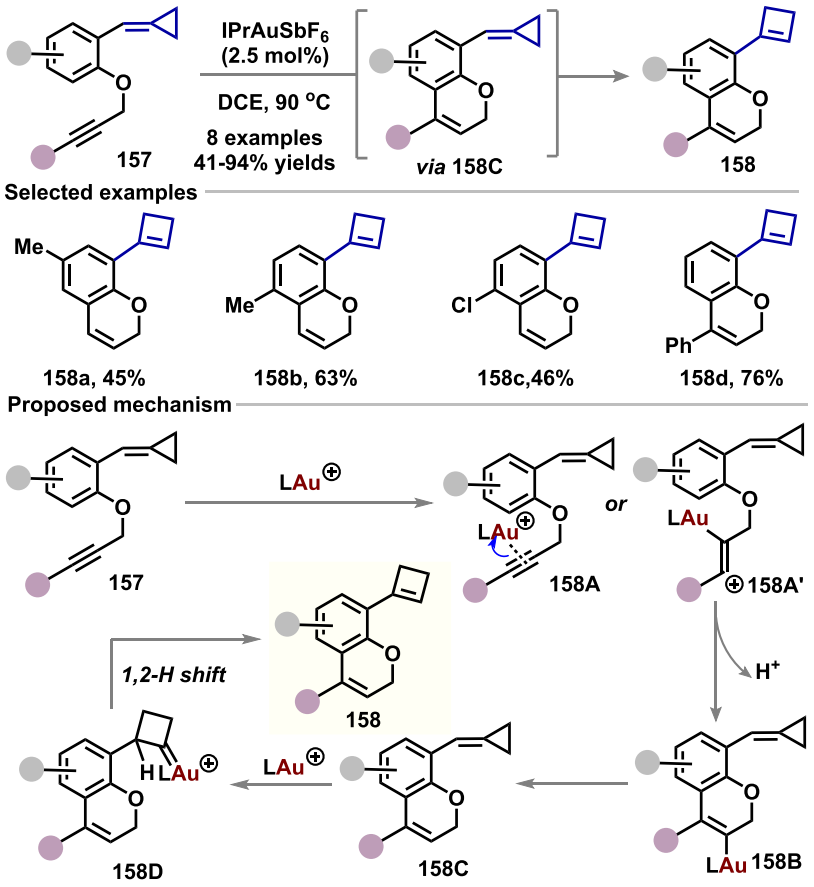
Scheme 49. Synthesis of Cyclobutenyl 2*H*-Chromene Derivatives from MCPs



In 2016, the Shi team further investigated the electrophilic nature of the Fischer type gold carbene derived from VDCPs (Scheme 53, **I**).[168] They designed an *ortho*-oxygen substituted VDCP substrate **168**, expecting the oxygen to engage as an intramolecular nucleophile with the gold carbene. Instead, under gold catalysis, *α*-methylenecyclobutanones **169** and **170** were obtained, indicating that the reaction proceeds *via* cyclobutyl−gold carbene intermediate **170C**, followed by C−O bond cleavage of the ether moiety to construct the cyclobutanone framework. Mechanistically, the Au(I) complex activates the allene moiety of the VDCP to generate the gold carbene specie **170C** *via* multiple sequence involving **170A** and **170B**. Intramolecular nucleophilic attack of the oxygen to the carbene center then forms the seven-membered oxonium intermediate **170D**. Subsequent cleavage of the C−O bond accompanied by dearomatization and elimination of Au^+L affords intermediate **170E**, which undergoes hydrolysis and keto−enol tautomerization to give the cyclobutanone intermediate **170G**. Meanwhile, the Au^+L species acts as a Lewis acid to promote aromatization *via* a 1,5-H shift to deliver product **170**. Remarkably, the *E*/*Z* stereoselectivity could be precisely modulated by the ligand: the bulky *N*-heterocyclic carbene (IPr) favored the *E*-isomer **169**, whereas the electron rich, sterically demanding phosphine BrettPhos delivered the *Z*-isomer **170**. The transformation tolerated a range of alkyl substituted VDCPs. In 2023, the authors extended this strategy to VDCPs **171** bearing tethered alcohol or amine nucleophiles (Scheme 53, **II**).[169] By fine-tuning tether length and sterics, gold(I) selectively activated the allene double bond proximal to the cyclopropane, forming intermediate **172A**. This triggered ring opening and expansion to gold carbene **172B**, which underwent intramolecular nucleophilic attack to give a zwitterionic species. Subsequent proton transfer furnished heterocyclic products **172** containing a cyclobutene unit.

To explore the synthetic potential of cyclobutylcarbenes generated from VDCPs, the Shi group introduced a benzyl ether moiety at the *ortho* position of the VDCP aryl ring **173** and developed a gold catalyzed asymmetric C(sp^3)−H insertion reaction, achieving highly enantioselective synthesis of benzoxepine derivatives **174** (Scheme 54).[170] The study revealed that the C−H insertion proceeded efficiently only when a strong electron withdrawing trifluoromethyl group was present at the *para* position of the benzene ring. The CF_3 enhances the acidity of the benzylic C−H bond, facilitating deprotonation and participation in a concerted insertion process, while also suppressing the formation of a potential benzylic cation intermediate, thereby avoiding competing benzyl migration pathways. A bulky monophosphine ligand directs substrate approach and governs enantioselectivity while effectively suppressing side reactions. Under these asymmetric conditions, a series of substrates afforded chiral benzoxepines (**174a−174d**) in good yields with excellent enantioselectivity. Mechanistically, the gold(I) catalyst first coordinates to the allene unit of the VDCP, activating it and driving cyclopropane ring expansion to generate the key cyclobutyl−gold carbene intermediate **174B**. Subsequent direct insertion of the adjacent benzylic C(sp^3)−H bond into the highly electrophilic carbene carbon **174C** then delivers the benzoxepine product **174**. This work not

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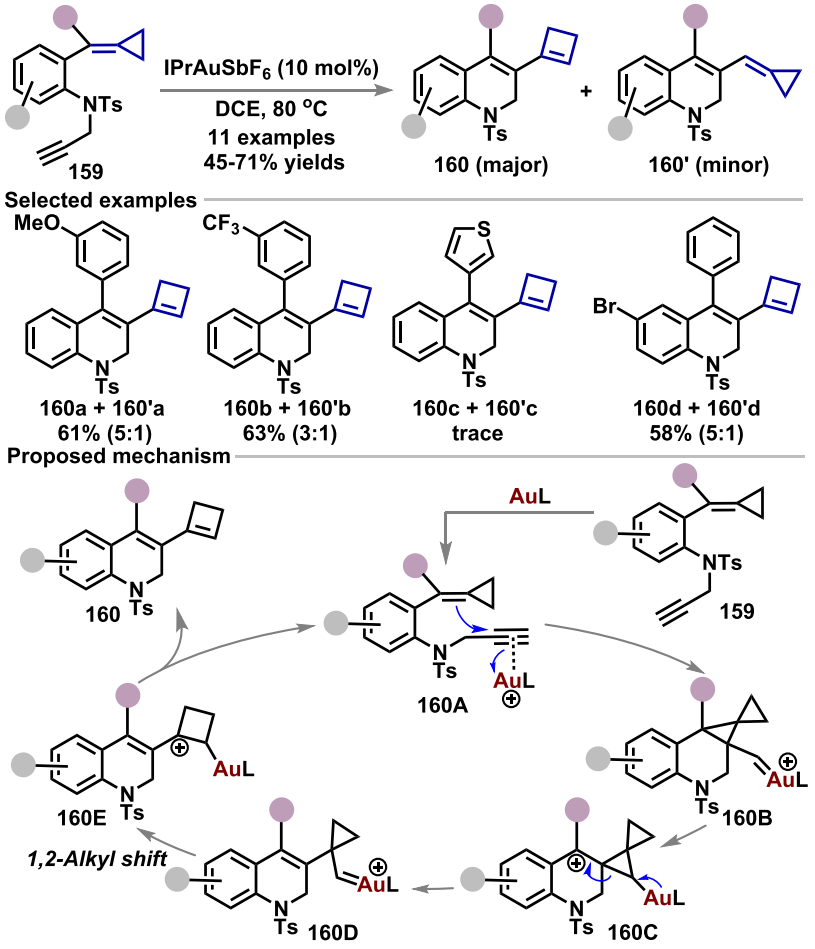
Scheme 50. Synthesis of Cyclobutenyl 1,2-Dihydroquinolines from MCPs



only demonstrates the diverse and tunable reactivity modes of VDCP derived gold carbenes but also highlights the considerable potential of VDCPs in asymmetric synthesis.

6. CONCLUSION AND PERSPECTIVE

Despite their demonstrated utility as versatile carbene precursors, the broader implementation of highly strained small-ring systems—including cyclopropenes, bicyclo[1.1.0]-butanes (BCBs), and [1.1.1]propellane (TCP)—remains constrained by synthetic accessibility and mechanistic limitations. Among these, cyclopropenes have been the most extensively studied, with well-established synthetic methods and a detailed understanding of their carbene reactivity. In contrast, BCBs and TCP are still in the early stages of exploration as carbene precursors, while methylenecyclopropanes and vinylidenecyclopropanes remain largely confined to intramolecular transformations under noble metal catalysis. Progress in this field will depend on the development of more general catalytic systems, deeper mechanistic insight—particularly in enantioselective contexts—and the integration of emerging activation strategies such as photoredox and electrochemical catalysis.

Beyond synthetic applications, these strained carbocycles possess untapped potential in materials science. While they have been utilized in medicinal chemistry and natural product synthesis, their incorporation into functional materials—such as strained polymers, molecular electronics, or stimuli-responsive systems—remains largely unexplored. Realizing such applications will require collaborative efforts between synthetic and materials chemists to leverage the unique structural and electronic properties of these motifs. Scalability represents another critical challenge. Current synthetic routes often involve multistep sequences and reliance on precious metal catalysts, raising concerns regarding cost, safety, and environmental impact. The development of efficient, economical, and sustainable synthetic methodologies is therefore essential for translating these systems from academic curiosities into practical tools.

In summary, strained small-ring carbocycles constitute a promising class of alternatives to conventional diazo-based carbene precursors, offering opportunities to expand synthetic methodology, explore new reactivity paradigms, and enable innovative applications in materials and industrial chemistry. As research in this field continues to progress, future efforts should focus on the development of efficient and sustainable synthetic strategies for constructing strained ring systems, while broadening their applicability across diverse reaction types, particularly with regard to enantiocontrol and sensitive functional group tolerance. Moreover, translating these systems into practical technologies offers great promise for the development of advanced functional materials and environmentally benign synthetic processes.

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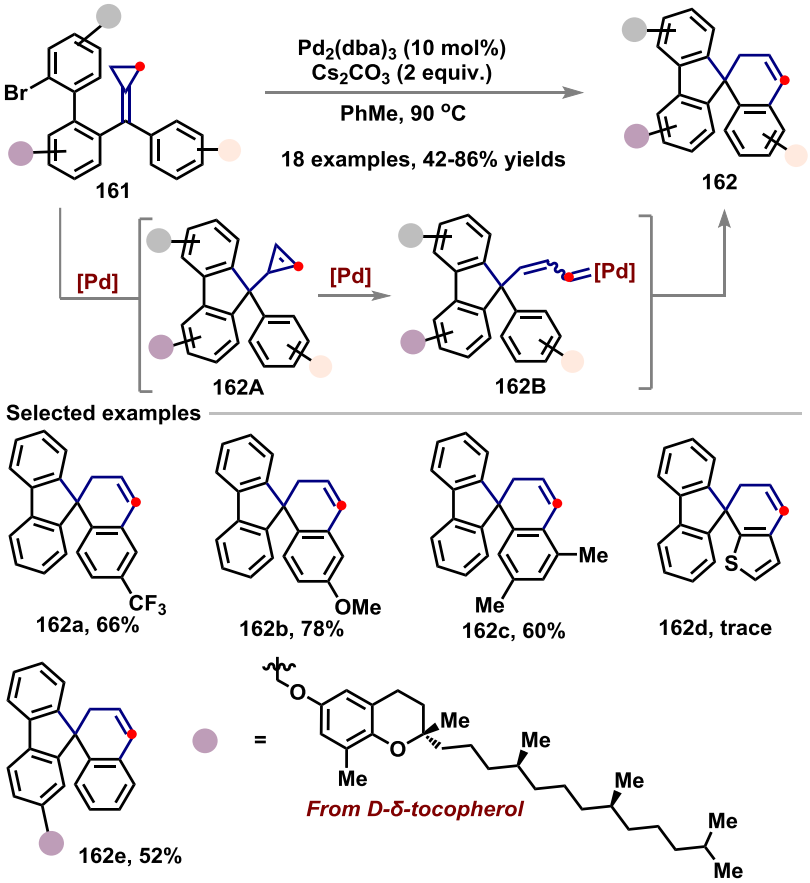
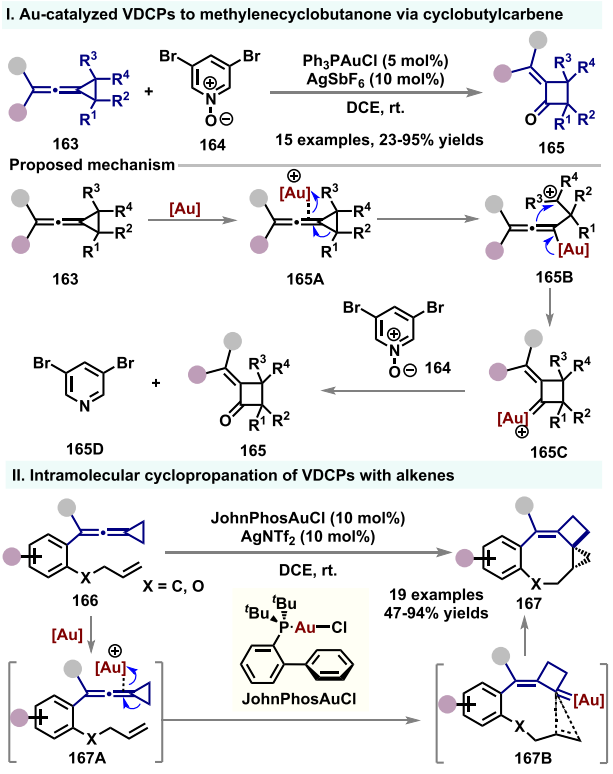
Scheme 51. Pd-Catalyzed Intramolecular Cyclization of MCPs towards Spirocycles



Scheme 52. Au-Catalyzed Ring-Opening of VDCPs as Carbene Precursors



AUTHOR INFORMATION

Corresponding Author

Yaojia Jiang − *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China;* orcid.org/0000-0003-0695-0069; Email: yjjiang@gzu.edu.cn

Authors

Fukuan Zhang − *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China*

Hui Wen − *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.5c09031

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge funding from the National Natural Science Foundation of China (22571055 and 22361010), the Central Government Guides Local Science and Technology Development Fund Projects [Qiankehezhongyindi (2023) 001], [Qiankehezhongyindi (2024) 007] and the Starting Funding of Research from Guizhou University.

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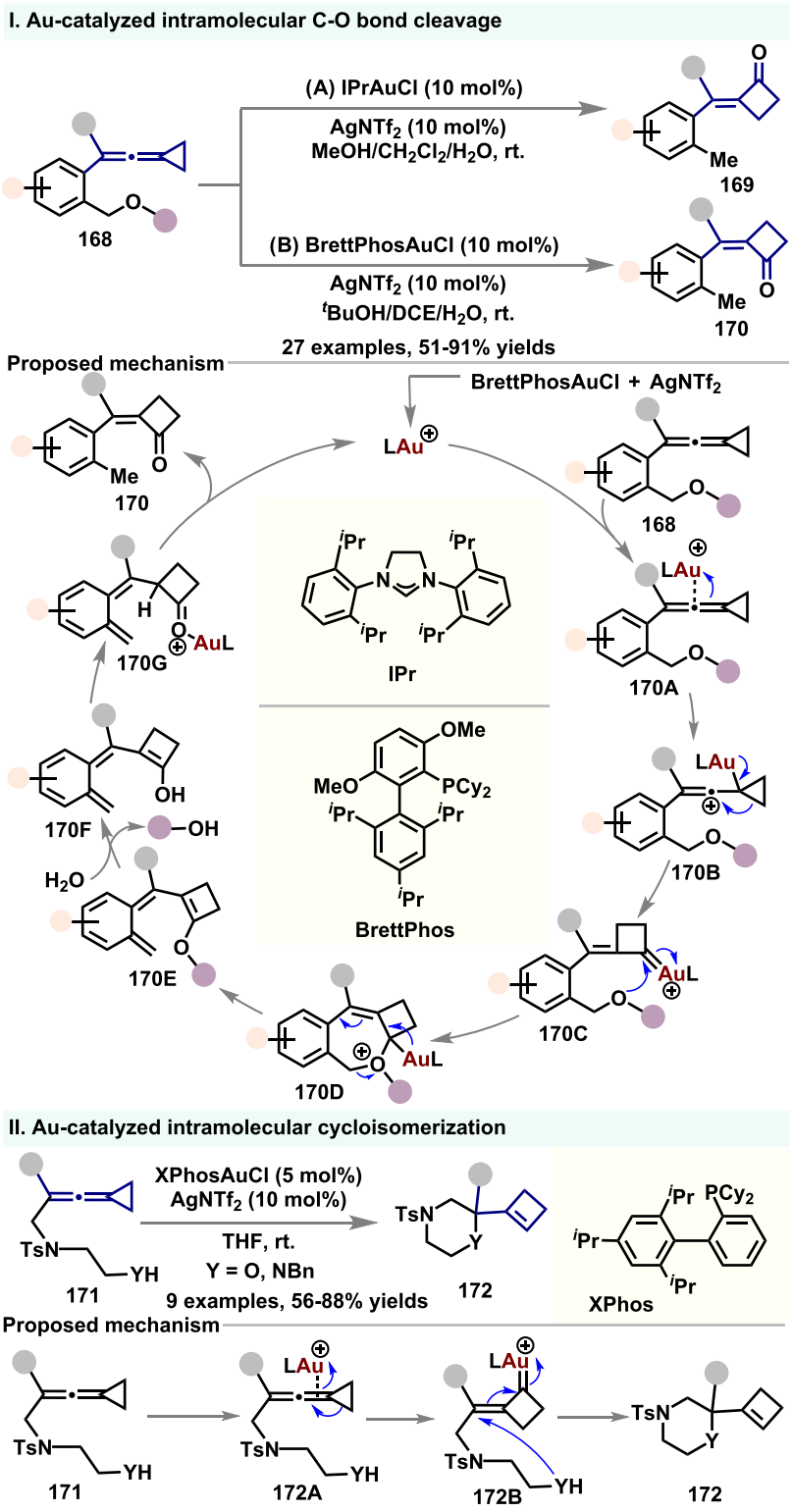
Scheme 53. Au-Catalyzed Intramolecular C−O Bond Cleavage and Cycloisomerization



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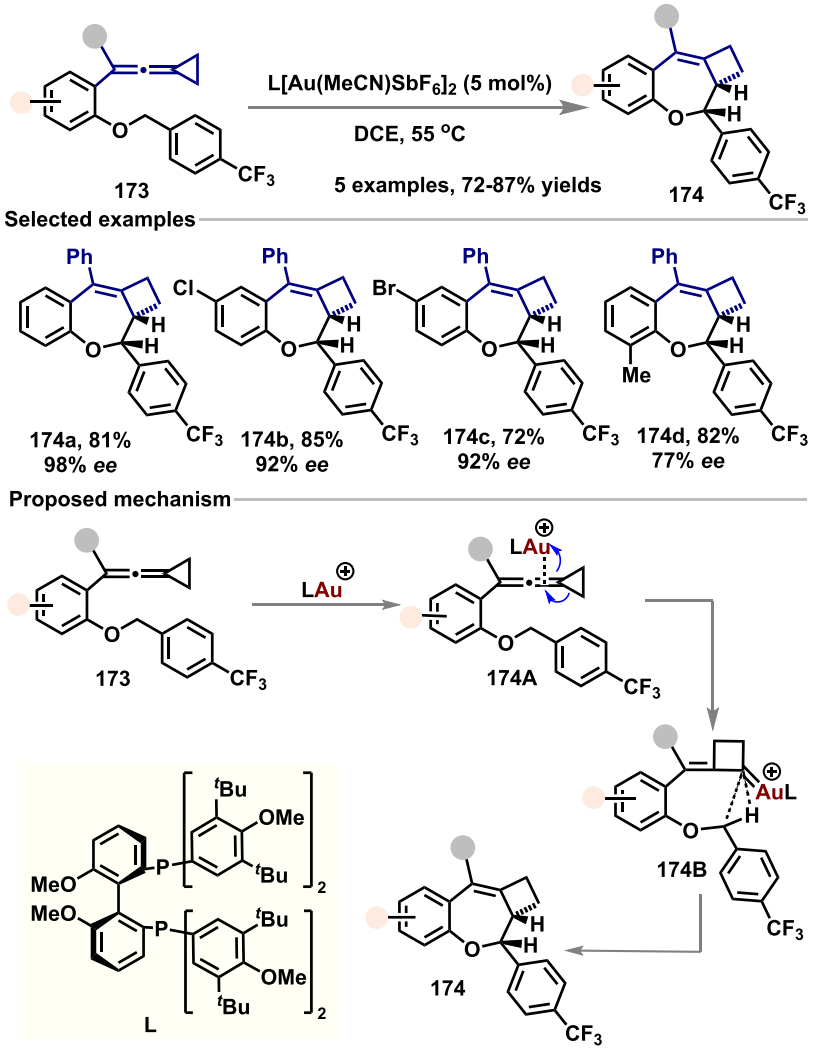
Scheme 54. Au-Catalyzed Asymmetric C−H Insertion of VDCPs



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