

Catalytic Asymmetric Cyclopropanations with Nonstabilized Carbenes

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ABSTRACT: Cyclopropanes are common building blocks in pharmaceuticals, agrochemicals, and organic materials. The most general methods for the synthesis of chiral cyclopropanes are catalytic additions of diazoalkanes to alkenes. However, a limitation of this approach is that diazoalkanes can only be safely handled on preparative scales if they possess stabilizing substituents. Here we show that *gem*-dichloroalkanes can serve as precursors to nonstabilized carbenes for asymmetric cyclopropanation reactions of alkenes. The process uses a cobalt catalyst and is proposed to involve the formation of a cationic carbenoid species bearing structural resemblance to the Simmons–Smith reagent. High levels of enantioselectivity are observed for monosubstituted, 1,1-disubstituted, and internal alkenes. The reaction is compatible with alkyl-substituted carbenes, which are susceptible to undergoing competing 1,2-hydride shifts.

Cyclopropanes are highly represented in pharmaceutical compounds¹ because of their unique three-dimensional structure and potential to engage in strain-induced ring-opening reactions. The most general approach to the synthesis of chiral cyclopropanes is the catalytic asymmetric addition of a diazoalkane to an alkene (Figure 1). Several classes of catalysts can perform this transformation, including chiral transition

metal complexes² and biocatalysts based on engineered P450 enzymes.³ Despite significant advances in this area, the reliance on diazoalkanes as carbene precursors poses significant liabilities. Diazo compounds are energetic molecules that require resonance stabilizing groups⁴ to be safely used on preparative scales. In the absence of these groups, strict engineering controls, such as *in situ* generation⁵ or continuous processing,⁶ are needed to mitigate the risk of violent exothermic decomposition.⁷

The Simmons–Smith reaction represents an alternative strategy for cyclopropanation that is particularly well-suited for the transfer of nonstabilized carbenes.⁸ In the Simmons–Smith reaction, a metal carbenoid is generated stoichiometrically from CH₂I₂ and a metal reductant such as Zn, Al, or Sm. Despite its over 50-year history in organic chemistry, asymmetric Simmons–Smith reactions are much less developed than diazoalkane-based cyclopropanations. Early efforts focused on the use of cleavable chiral auxiliaries⁹ or stoichiometric chiral promoters.¹⁰ Catalytic asymmetric variants have since been demonstrated but are largely restricted to allylic alcohols.¹¹ A notable exception is Shi's dipeptide ligand system,¹² which does not require a directing group but has limited functional group compatibility.

All of the current catalytic asymmetric Simmons–Smith reactions rely on intercepting the intermediate zinc carbenoid with a chiral Lewis acid.¹³ The central challenge is the high background reactivity of the achiral zinc carbenoid, which often necessitates stoichiometric loadings of the chiral Lewis

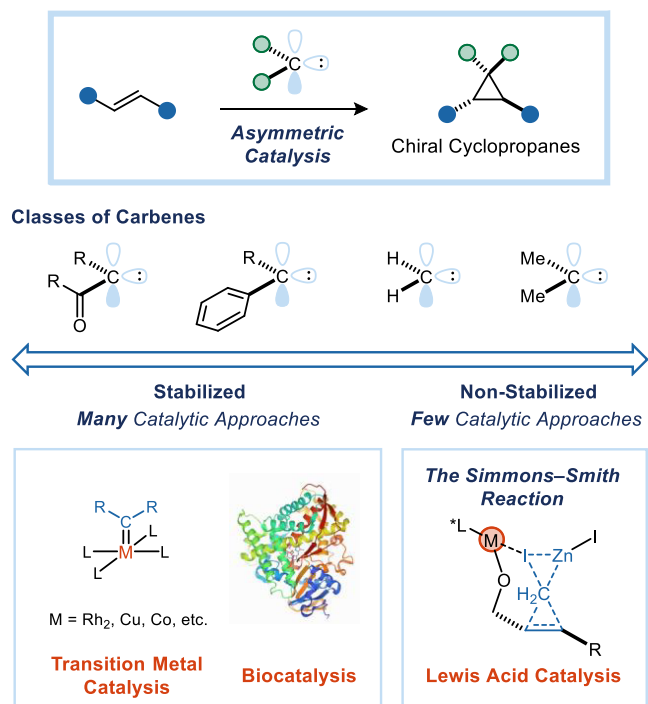
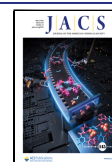


Figure 1. Catalytic asymmetric cyclopropanation reactions with stabilized and nonstabilized carbenes.

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acid or a directing group to preassociate the Lewis acid with the substrate. To circumvent this problem, we recently proposed an alternative mode of catalysis in which a transition metal carbenoid is generated from the oxidative addition of a CR_2X_2 reagent.¹⁴ Here we show that this approach provides a general entry into catalytic asymmetric cyclopropanations. Notably, the cobalt-catalyzed cyclopropanation allows for the transfer of alkyl-substituted carbenes,¹⁵ a process that is not efficient under Simmons–Smith conditions, even in a non-asymmetric context.

The dimethylcyclopropanation of model 1,3-diene **1** can be carried out in 95% yield using 2,2-dichloropropane, Zn, and (PDI)CoBr₂ catalyst **3** (PDI = pyridine diimine) (Figure 2).

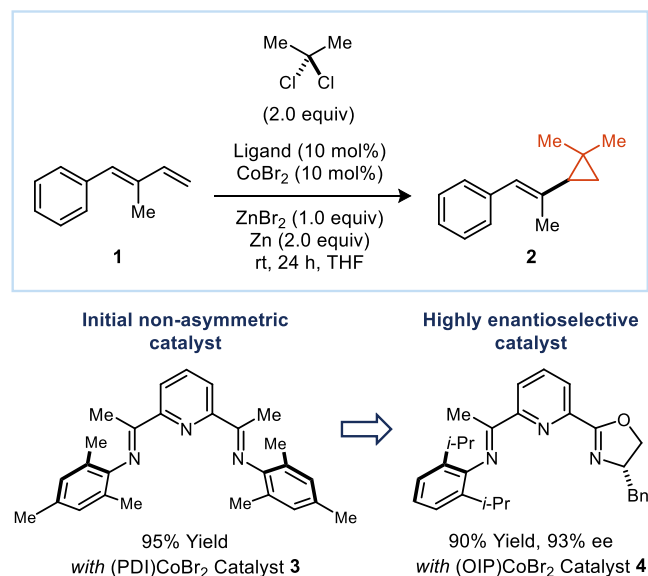


Figure 2. A chiral cobalt catalyst for the asymmetric reductive cyclopropanation of alkenes using *gem*-dichloroalkanes.

With chiral pyridine bis(oxazoline) (Pybox) ligands, it was possible to obtain moderate levels of enantioselectivity (up to 45% ee). However, further optimization efforts using this ligand class were hampered by consistently low yields of cyclopropanation (<28%). Recognizing the high sensitivity of the reaction to the steric profile of the catalyst, we reasoned that C₁-symmetric ligands¹⁶ retaining the hindered aryl substituent might prove to be more promising. Accordingly, we identified the (OIP)CoBr₂ complex **4** (OIP = oxazoline iminopyridine) as an effective catalyst, providing dimethylcyclopropane **2** in 90% yield with 93% ee.

The substrate scope of the catalytic asymmetric dimethylcyclopropanation is summarized in Table 1. Whereas the non-asymmetric reaction using (PDI)CoBr₂ catalyst **3** was largely limited to 1,3-diene substrates, (OIP)CoBr₂ catalyst **4** displays a much broader scope that includes several classes of monoalkenes. The mode of asymmetric induction relies on the presence of a branched carbon on one side of the double bond, and substrates that fulfill this criterion reliably provide ee values in the >80% range. For example, styrenes and their heterocyclic derivatives are effective substrates. 1,1-Disubstituted and (*Z*)-1,3-disubstituted alkenes may also be used, including those containing indane or tetralin ring systems. The reaction tolerates protic functionality, such as a free phenol and an unprotected indole. Thioethers do not undergo competing ylide formation, and no competing insertions into C–B bonds

or epoxides were observed. Finally, aryl bromides, which are susceptible to oxidative addition by low-valent metal catalysts, are compatible with the reaction conditions.

The cobalt-catalyzed cyclopropanation is insensitive to electronic effects and provides high yields for both electron-rich and electron-deficient alkenes. By contrast, the catalyst, being quite hindered, is exceptionally sensitive to the steric properties of the alkene. Monosubstituted alkenes react at the highest rates, followed by (*Z*)-1,2-disubstituted and 1,1-disubstituted alkenes. (*E*)-1,2-Disubstituted alkenes react sluggishly but in some limited cases can be used. For example, a dienyl ester substrate yields the pyrethroid precursor ethyl chrysanthemate (**14**) with 97% ee.

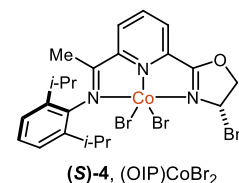
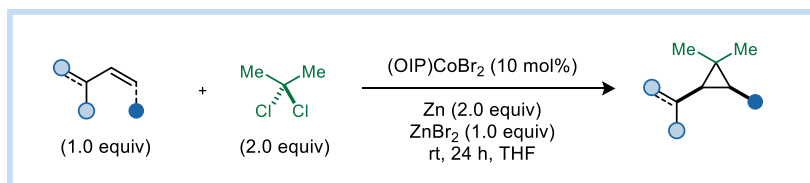
The sensitivity to the substitution pattern of the alkene can be exploited to achieve selective monocyclopropanations of terpenoid polyalkenes. One instructive case is that of myrcene. In the cobalt-catalyzed cyclopropanation, the product is predominantly a single regioisomer (**25**) (10:1 rr). Under Simmons–Smith conditions using 1 equiv of a zinc carbenoid, all three monocyclopropane regioisomers are formed, alongside double and triple cyclopropanation products.¹⁷

Recognizing the potential value of sp³-rich polycyclic frameworks in drug discovery,¹⁸ we sought to apply this reaction to the synthesis of chiral spirocyclopropanes (Figure 3A).¹⁹ The requisite *gem*-dichlorocycloalkanes can be readily synthesized in one step from their corresponding cyclic ketones using WCl₆.²⁰ With little modification to the reaction conditions, spirocyclopropanes **30–37** were prepared with high levels of enantioselectivity.

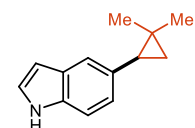
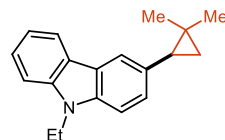
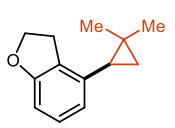
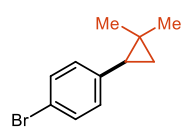
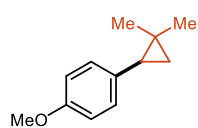
Vinylcyclopropanes are valuable starting materials for transition-metal-catalyzed ring-opening reactions.²¹ Access to vinylcyclopropanes in highly enantioenriched form provided us with an opportunity to examine the extent of chirality transfer when these intermediates are transformed into larger rings (Figure 3B). We selected catalytic 1,3-rearrangement²² and [5 + 1] cycloaddition²³ reactions as targets because they proceed through organometallic oxidative addition/reductive elimination mechanisms with the potential to preserve stereochemistry. In both cases, the ee of the vinylcyclopropane was retained with high fidelity, providing a straightforward entry into chiral five- and six-membered rings.

As an alternative to heterogeneous reduction with Zn powder, the asymmetric cyclopropanation can also be carried out under homogeneous conditions using a tertiary amine as the reductant in combination with a photoredox cocatalyst and visible-light irradiation (Figure 4A).²⁴ Notably, the inexpensive organic dye eosin Y proved to be effective and outperformed several commonly used precious metal Ru and Ir catalysts. Interestingly, under photoredox conditions, no yield of cyclopropane was observed without the inclusion of a ZnX₂ additive. However, reactions conducted with ZnI₂ (3.0 equiv) provided product **10** with a level of enantioselectivity similar to that observed under the standard catalytic conditions. This result suggests that the ZnX₂ byproduct generated under Zn reduction conditions may be noninnocent in the mechanism.

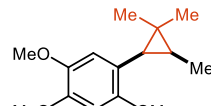
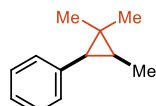
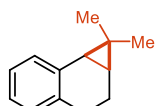
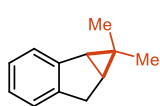
To further probe the role of ZnX₂, single-turnover experiments were carried out in the absence of any external reductants. Cyclic voltammetry experiments indicated that the Co(II) complex undergoes a one-electron reduction at $E_{1/2} = -1.18$ V vs Cp₂Fe/Cp₂Fe⁺. This wave displays a large peak-to-peak separation due to the coupled Br[−] dissociation step. When ZnBr₂ is present, the reduction wave of the Co(II) complex shifts anodically by 230 mV, which we attribute to

Table 1. Substrate Scope Studies^a

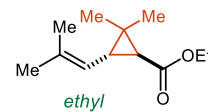
Monosubstituted Alkenes



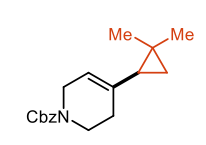
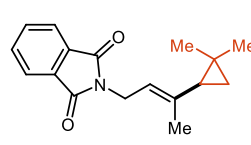
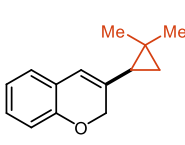
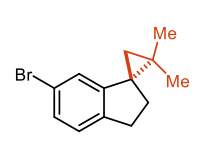
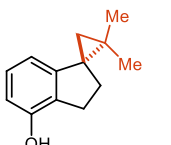
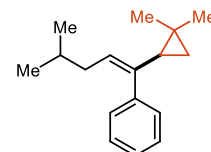
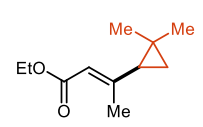
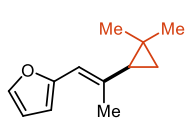
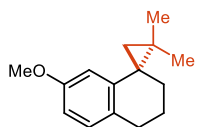
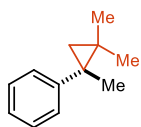
(Z)-Alkenes



(E)-Alkene

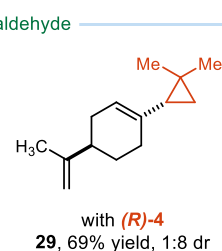
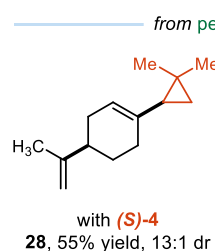
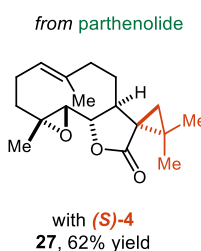
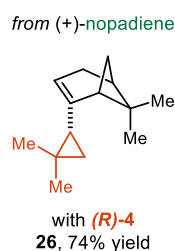
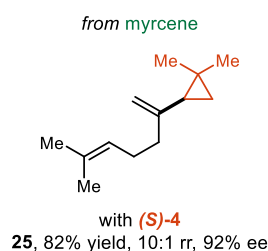


1,1-Disubstituted Alkenes



1,3-Dienes

Monocyclopropanation of Terpene Polyalkenes



^aIsolated yields were obtained following purification. Enantiomeric excess (ee) values were determined by GC or HPLC analysis using chiral columns. See the Supporting Information for detailed procedures. ^bAn additional 10 mol % portion of catalyst 4 was added. The total reaction time was 48 h. ^cThe absolute configuration of product 23 was assigned by X-ray crystallography. The enantiomeric excess in parentheses was measured following crystallization.

ZnBr₂ assisting in ionization through the formation of ZnBr₃⁻. The authentic Co(I) complex 44 was prepared by treating Co(II) complex 4 with NaEt₃BH (Figure 4A).²⁵ When Co(I) complex 44 was treated with 1 and 2,2-dichloropropane, no cyclopropanation was observed. However, carrying out the same stoichiometric reaction with ZnBr₂ gave a 60% yield of cyclopropane 2 (yield based on 2 equiv of Co(I) required for every equivalent of cyclopropane formed). These results show that ZnBr₂ is not only involved in facilitating the reduction of

Co(II) to Co(I) but is also required to generate the active carbenoid intermediate responsible for cyclopropanation.

With these mechanistic insights, we hypothesize that cyclopropanation proceeds by a Co(II)/Co(I) catalytic cycle (Figure 4B). Activation of Me₂CCl₂ by the Co(I) species likely occurs through a radical Cl abstraction mechanism. The less hindered CH₂Cl₂ is unreactive in the cyclopropanation, which would be inconsistent with a concerted oxidative addition mechanism but in accordance with radical stability trends. A

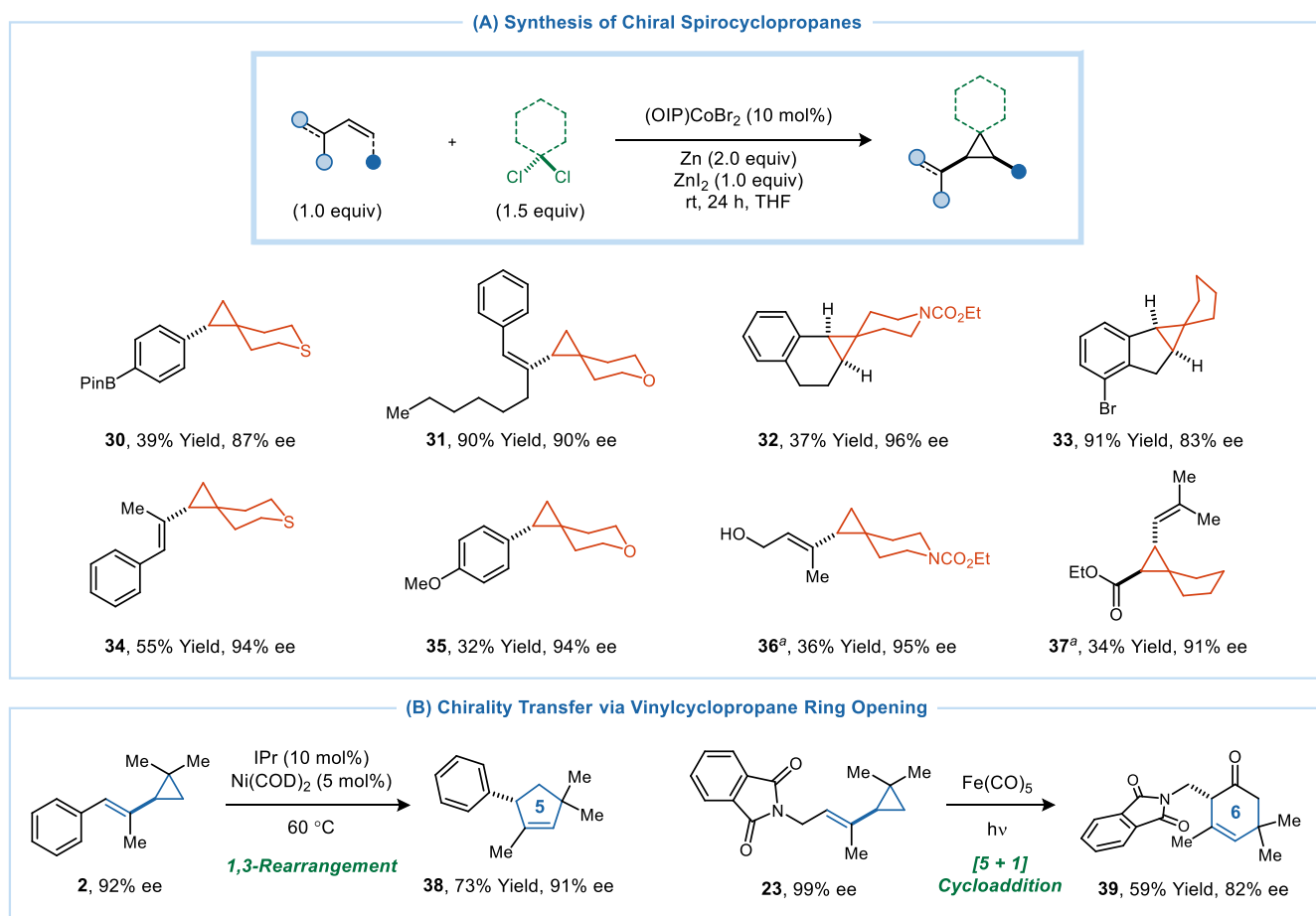


Figure 3. Synthetic applications of the asymmetric cyclopropanation. (A) Synthesis of chiral spirocyclopropanes using *gem*-dichloro reagents derived from cyclic ketones. (B) Chirality transfer processes for the asymmetric synthesis of larger rings from vinylcyclopropanes. ^aAn additional 10 mol % portion of catalyst **4** was added. The total reaction time was 48 h.

radical mechanism for C–Cl cleavage would explain the tolerance for C(Ar)–Br bonds in the substrate scope. Cyclopropanations with CH_2Br_2 are high-yielding but generally provide low levels of enantioselectivity with catalyst **4**.

Capture of the $\text{Me}_2\text{C}\cdot\text{Cl}$ radical by Co(I) would generate a putative $\text{Co}(\text{CMe}_2\text{Cl})(\text{Cl})$ species (**45**). According to DFT models, transfer of the Me_2C fragment to styrene is energetically feasible and has a barrier of only 16.4 kcal/mol (Figure 4B). Alternatively, abstraction of Cl^- by the ZnX_2 Lewis acid forms a cationic $[\text{Co}(\text{CMe}_2\text{Cl})]^+$ species (**46**), and the barrier for Me_2C transfer to styrene further decreases to 14.7 kcal/mol. Notably, related cationic Co(II) alkyl species are proposed to be intermediates in olefin polymerization reactions catalyzed by related complexes.²⁶

Metal carbenoids can be placed on a structural continuum between limiting $\text{M}-\text{CR}_2\text{X}$ (haloalkyl) and $\text{X}-\text{M}=\text{CR}_2$ (carbene) forms (Figure 4C). Previous computational studies suggest that the propensity of a metal carbenoid to undergo carbene transfer is positively correlated with the degree of carbene character.^{8d} For example, LiCH_2Cl has a high degree of carbene character, as evidenced by an acute Li–C–Cl bond angle. The calculated barrier for CH_2 transfer from LiCH_2Cl to ethylene is only 3.8 kcal/mol. By comparison, ClZnCH_2Cl has a more obtuse Zn–C–Cl angle and has a higher barrier for CH_2 transfer (13.1 kcal/mol). The previously isolated (PDI)Rh(CH_2Cl) species **47** lies firmly in the haloalkyl form and is not known to engage in cyclopropanation reactions.²⁷

An inspection of the optimized structure for the neutral carbenoid species **45** reveals a Co–C–Cl angle of 95° and a Co–C distance of 1.97 Å. Upon Cl^- abstraction to generate cationic carbenoid **46**, the lower coordination number and increased electrophilicity of Co cause the Co–C–Cl angle to decrease to 78° . This decrease in angle is accompanied by a decrease in the Co–C distance to 1.93 Å, which is indicative of partial π -bonding character. Cyclopropanation reactions of zinc carbenoids rely on two primary frontier orbital interactions: donation of the alkene π electrons into the C–X σ^* orbital and donation of the Zn–C σ bond into the alkene π^* orbital. Analogous orbitals can be located for the optimized structure of cationic carbenoid **46** (Figure 4B). An orbital with Co–C σ -bonding character can be found at HOMO–8, and the C–Cl σ^* orbital appears at LUMO+8.

Finally, DFT models provide a hypothesis for the origin of asymmetric induction (Figure 4D). In the lowest-energy transition state for the cyclopropanation of styrene with the cationic carbenoid **46**, styrene approaches the carbene on the same side as the Bn group of the oxazoline. This approach initially seemed counterintuitive but, on closer inspection, allows the large dimethylcarbenoid to be situated on the less hindered face of the catalyst. The second consideration is the orientation of the Ph group of styrene, which is pointed away from the *N*-(*i*-Pr)₂Ph substituent of the catalyst in the lowest-energy transition state.

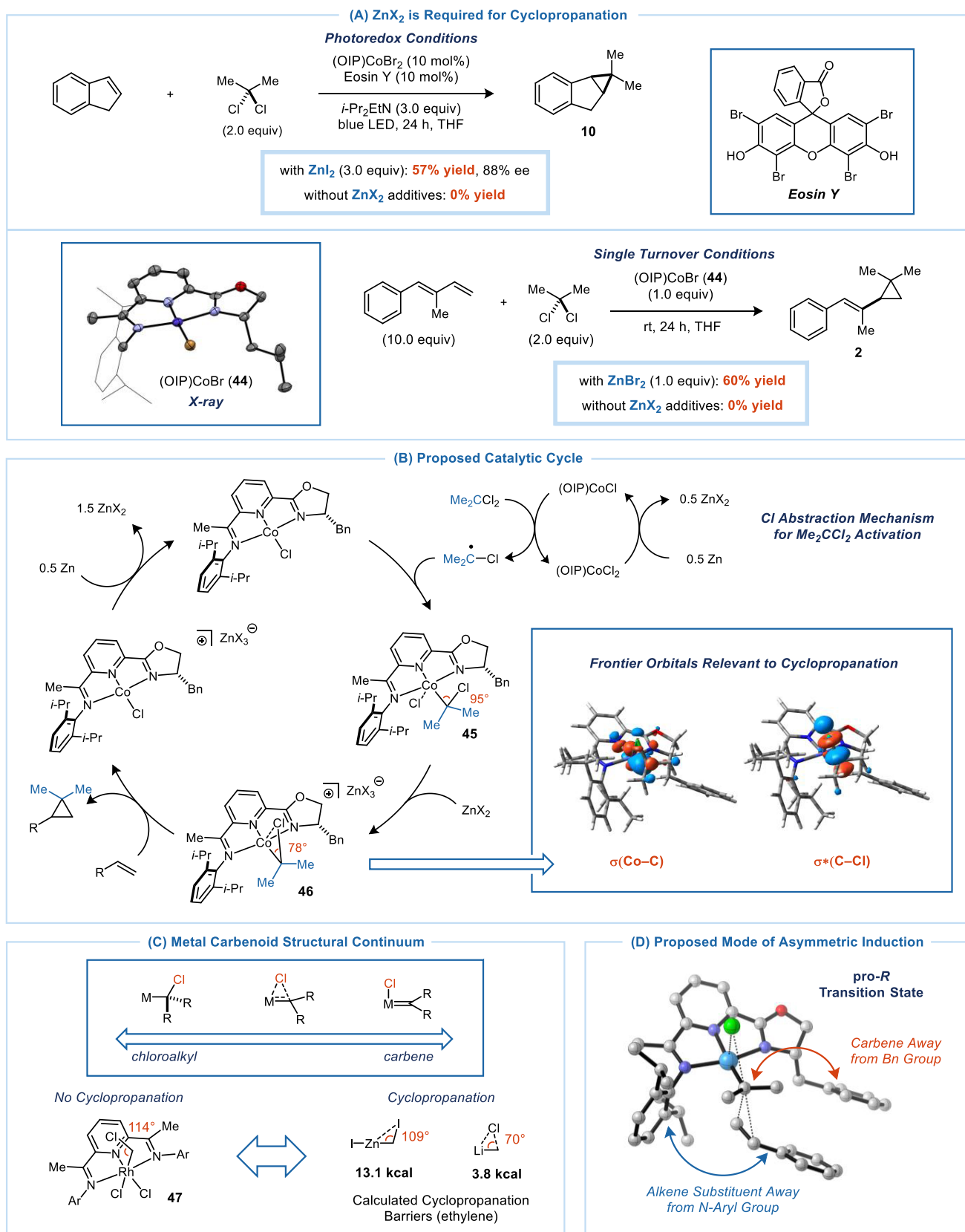


Figure 4. Mechanistic studies. (A) ZnX_2 is critical for efficient cyclopropanation. (B) A proposed mechanism for CR_2 transfer. (C) The propensity of a metal carbenoid to undergo CR_2 transfer is correlated to the degree of carbene vs haloalkyl character. (D) Proposed origin of the enantioselectivity based on DFT models. See the [Supporting Information](#) for details regarding computational methods.

In summary, reactive transition metal carbenoids can be generated from the activation of readily available and

nonenergetic dihaloalkane reagents. This process significantly expands the scope of metal carbenoids that may engage in

reductive carbene transfer reactions beyond the zinc carbenoids used in the canonical Simmons–Smith process. By using chiral ligands on cobalt, highly enantioselective cyclopropanations can be carried out without the substrate scope limitations imposed by chiral Lewis acid catalysis.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c01949>.

Experimental details, characterization data, and computational details (PDF)

Accession Codes

CCDC 2226831 and 2226832 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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