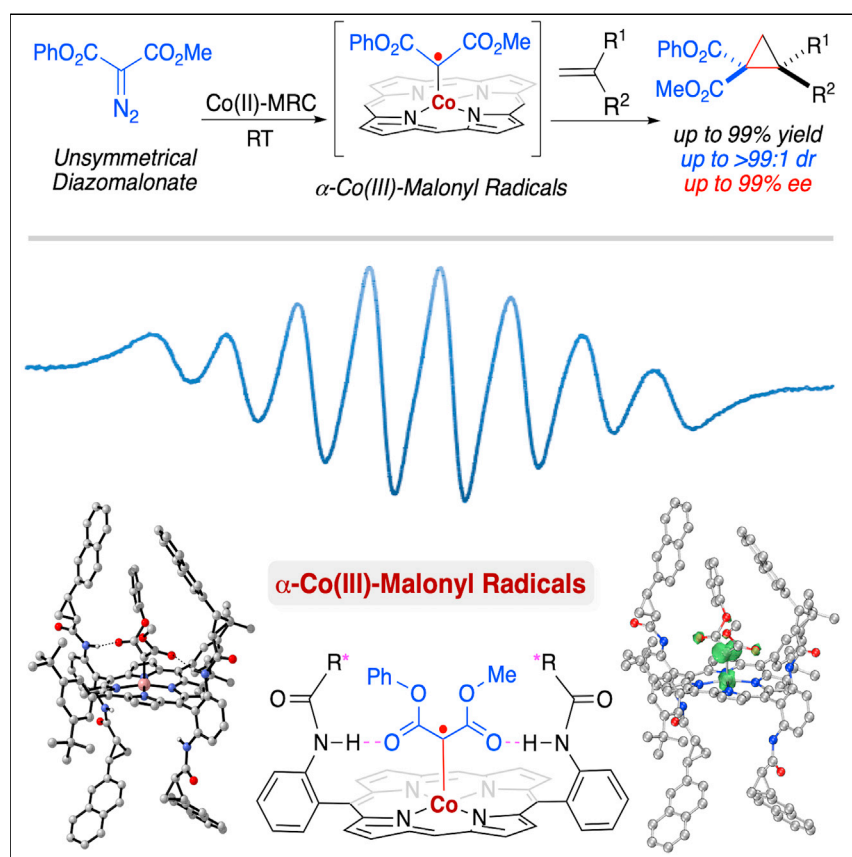


Article

Radical differentiation of two ester groups in unsymmetrical diazomalonates for highly asymmetric olefin cyclopropanation



Cobalt(II)-based metalloradical catalysis (MRC) has been successfully applied for the development of the first catalytic system that is highly effective for asymmetric olefin cyclopropanation with unsymmetrical diazomalonates, a class of stable diazo compounds that have not been previously utilized. Supported by an optimal *D*₂-symmetric chiral amidoporphyrin ligand, the Co(II)-based catalytic system is generally applicable to a broad range of olefin substrates with different functionalities, enabling stereoselective synthesis of diverse 1,1-cyclopropanediester in high yields with both excellent diastereoselectivity and enantioselectivity.

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Highlights

Highly asymmetric system for cyclopropanation with unsymmetrical diazomalonates

Asymmetric synthesis of 1,1-cyclopropanediester from different types of alkenes

Detailed mechanistic studies on elucidation of underlying stepwise radical pathway

Importance of noncovalent attractive interactions in metalloradical catalyst design



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Article

Radical differentiation of two ester groups in unsymmetrical diazomalonates for highly asymmetric olefin cyclopropanation

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SUMMARY

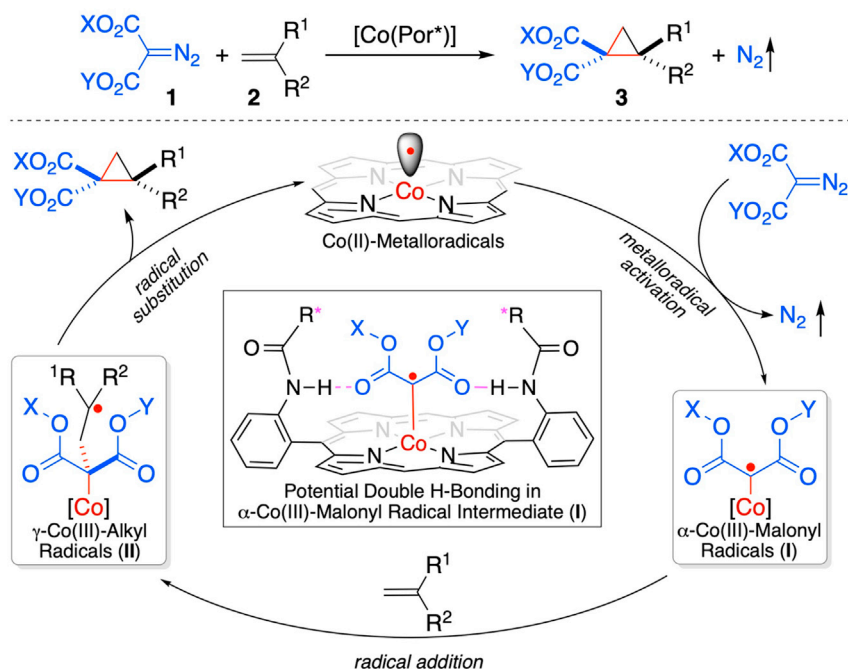
Diazomalonates have been demonstrated as effective metalloradicalophiles for asymmetric radical olefin cyclopropanation via Co(II)-metalloradical catalysis (MRC). Supported by *D*₂-symmetric chiral amidoporphyrin ligand, Co(II)-based metalloradical system can efficiently activate unsymmetrical methyl phenyl diazomalonate (MPDM) with effective differentiation of the two ester groups for asymmetric cyclopropanation, enabling stereoselective construction of 1,1-cyclopropanediastereomers bearing two contiguous chiral centers, including all-carbon quaternary stereogenic center. The Co(II)-catalyzed asymmetric cyclopropanation, which operates at room temperature without slow addition of the diazo compound, is generally applicable to broad-ranging olefins and tolerates various functionalities, providing a streamlined synthesis of chiral 1,1-cyclopropanediastereomers in high yields with both high diastereoselectivity and enantioselectivity. Combined computational and experimental studies support the underlying stepwise radical mechanism for Co(II)-catalyzed cyclopropanation. In addition to functioning as 1,3-dipoles for forming five-membered structures, enantioenriched (*E*)-1,1-cyclopropanediastereomers serve as useful building blocks for stereoselective synthesis of different cyclopropane derivatives. In addition, the enantioenriched (*E*)-1,1-cyclopropanediastereomers can be stereoselectively converted to (*Z*)-diastereomers.

INTRODUCTION

Radical reactions, in contrast to polar reactions, have not been widely employed as synthetic tools for organic synthesis despite their unique profile of reactivity and selectivity as well as attractive set of attributes and characteristics.^{1–8} This predicament is ascribed to the well-known challenges associated with the high reactivity of most radical intermediates. The resurgence of photoredox catalysis has recently evoked enormous interest of synthetic chemists in manipulating reactivity and even stereoselectivity of radical reactions.^{9–23} As a conceptually different approach to harness the potential of radical reactions for stereoselective organic synthesis, metalloradical catalysis (MRC) utilizes metal-centered d-radicals to launch as well as to control the reactivity and selectivity of radical processes in a catalytic fashion without the use of light or an external initiator.^{24–43} Cobalt(II) complexes of porphyrins, as stable 15e-metalloradicals, enjoy an unusual capability of activating diazo compounds as radical precursors to generate α -Co(III)-alkyl radicals that can serve as key intermediates for achieving catalytic radical transformations. Particularly, cobalt(II) complexes of *D*₂-symmetric chiral amidoporphyrins [Co(*D*₂-Por*)] have been demonstrated as effective metalloradical catalysts for asymmetric radical cyclopropanation of alkenes

The bigger picture

Optically active 1,1-cyclopropanediastereomers represent an important class of chiral building blocks that have found wide-ranging synthetic applications. Guided by the principles of metalloradical catalysis, we have successfully developed Co(II)-based metalloradical system that can use unsymmetrical diazomalonates as effective metalloradicalophiles for asymmetric radical cyclopropanation, enabling synthesis of 1,1-cyclopropanediastereomers bearing two contiguous stereogenic centers in high yields with both excellent diastereoselectivity and enantioselectivity. This Co(II)-catalyzed cyclopropanation, which operates at room temperature, is generally applicable to broad-ranging alkenes and tolerates various functionalities. Combined experimental and computational studies have shed light on the underlying stepwise radical mechanism involving α -Co(III)-malonyl radicals as the key intermediate. We show the importance of cooperative noncovalent interactions in the development of the catalytic system.



Scheme 1. Working proposal for cyclopropanation of alkenes with diazomalonates via Co(II)-based metalloradical catalysis

with different types of diazo compounds.^{44–59} Combined experimental and computational studies support a stepwise radical mechanism of the Co(II)-based cyclopropanation where α-Co(III)-alkyl radical intermediates are often stabilized by potential H-bonding interactions between N–H moieties of the chiral amide units of the porphyrin ligands as H-bond donors and carbonyl groups (or heteroatoms) on the radical precursors as H-bond acceptors.^{60–62} This H-bonding interaction enhances the catalytic reactivity while rigidifying the system to improve stereoselectivity. Given that asymmetric olefin cyclopropanation with diazomalonates is an important transformation with unaddressed issues, we were prompted to explore a potential solution via Co(II)-MRC on the supposition that the generation and stabilization of the corresponding α-Co(III)-malonyl radicals I would be significantly facilitated by the double H-bonding interactions (Scheme 1). More challengingly, if unsymmetrical diazomalonates are used, could the stereochemistry of the two newly formed chiral centers in the resulting 1,1-cyclopropanediester be controlled? Considering that the two substituents in intermediate I are both ester groups, could the incoming olefin effectively differentiate the two pro-chiral faces of the Co-supported C-centered radical for enantioselective generation of the first stereocenter (Scheme 1)? For the same consideration, could the two similar ester substituents effectively discriminate the two pro-chiral faces of the γ-Co(III)-alkyl radical II during 3-exo-tet radical cyclization for diastereoselective C–C bond formation (Scheme 1)? If these challenges could be addressed through the use of proper [Co(D₂-Por*)] catalyst, it would lead to the development of a new catalytic system for asymmetric cyclopropanation of alkenes with unsymmetrical diazomalonates to construct optically active 1,1-cyclopropanediester, which have been demonstrated as versatile building blocks for wide-ranging synthetic applications.^{63–116}

Catalytic cyclopropanation of alkenes with diazomalonates presents a potentially attractive approach for the synthesis of the highly valuable 1,1-cyclopropanediester

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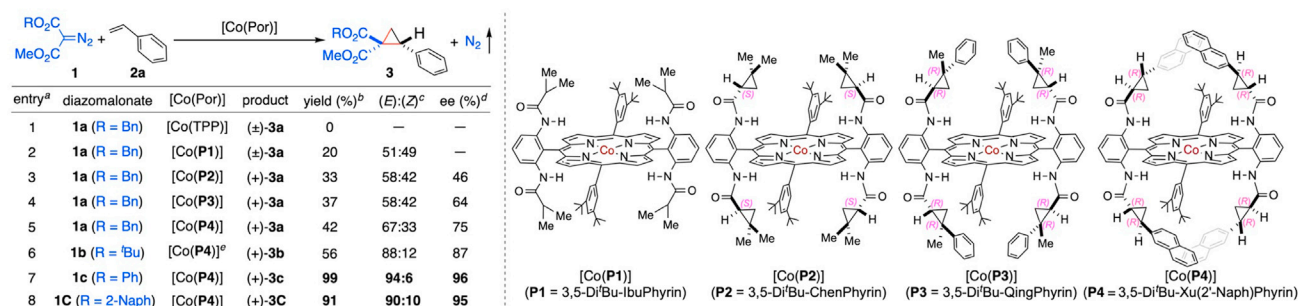


Figure 1. Ligand effect on Co(II)-based catalytic system for cyclopropanation of styrene with unsymmetrical diazomalonates

^aCarried out with diazomalonates 1 (0.10 mmol) and 2a (0.12 mmol) in toluene at room temperature for 24 h in one-time fashion without slow addition using [Co(Por)] (2 mol %) under N₂. ^bIsolated yields. ^cDiastereomeric ratio (dr) determined by ¹H-NMR. ^dEnantiomeric excess (ee) determined by chiral HPLC. ^eUsing [Co(Por)] (5 mol %).

with a possibility of controlling stereoselectivity.^{117–128} Because of their low reactivity and inherent challenge of stereocontrol associated with the two similar electron-withdrawing ester groups, the use of diazomalonates as carbene precursors for asymmetric olefin cyclopropanation by existing catalytic systems has been limited with substrate scope and hampered by low enantioselectivity.^{117–120,123,124} Hence, the corresponding phenyliodonium ylides, a class of alternative reagents that are more reactive but less stable and difficult to prepare, have been utilized as the surrogates of diazomalonates for olefin cyclopropanation to synthesize 1,1-cyclopropanediester with generation of stoichiometric amount of iodobenzene as a byproduct.^{122,126–128} To the best of our knowledge, unsymmetrical diazomalonates have not been previously employed for asymmetric olefin cyclopropanation.^{119,126,128} We herein report the development of the first catalytic system via Co(II)-based MRC that is highly effective for asymmetric cyclopropanation of alkenes using unsymmetrical diazomalonates with effective differentiation of the two ester groups. We describe the significant ligand effect on the Co(II)-catalyzed cyclopropanation, leading to the identification of a suitable D₂-symmetric chiral amidoporpyrin for the catalytic process. We show that the optimized catalytic system is remarkably general and can be efficiently applied to a broad range of alkenes, affording various 1,1-cyclopropanediester in high yields with effective control in both diastereoselectivity and enantioselectivity of the two newly constructed contiguous chiral centers. Among other attributes, the Co(II)-based metalloradical system is highlighted by a high degree of functional group tolerance. In addition to demonstrating the synthetic utility of the enantioenriched 1,1-cyclopropanediester products, we present experimental evidence that agrees with the underlying stepwise radical mechanism for the Co(II)-based catalytic system.

RESULTS AND DISCUSSION

Reaction development

Our study began with the investigation of catalytic cyclopropanation reaction of styrene (2a) with the unsymmetrical benzyl methyl diazomalonate (1a) (Figure 1). It was found that [Co(TPP)] (TPP = 5,10,15,20-tetraphenylporphyrin), the simple Co(II)-metalloradical catalyst, was inactive for the transformation, failing to provide any of the desired 1,1-cyclopropanediester 3a (Figure 1, entry 1). However, with the use of achiral amidoporpyrin catalyst [Co(P1)] (P1 = 3,5-Di^tBu-IbuPhyrin),¹²⁹ the reaction could proceed at room temperature and deliver the desired cyclopropane product 3a in low but significant yield (Figure 1, entry 2). The difference in catalytic activity between [Co(TPP)] and [Co(P1)] signifies the importance of the proposed double

H-bonding interactions in activating and stabilizing the α -Co(III)-malonyl radical intermediate I (Scheme 1). On the other hand, the formation of cyclopropane **3a** in almost equal ratio of (E)- and (Z)-diastereomers (Figure 1, entry 2) clearly indicates the aforementioned challenge associated with the differentiation of the two similar ester groups during the catalytic process. When using first-generation chiral metal-loradical catalyst [Co(P2)] (P2 = 3,5-Di^tBu-ChenPhyrin),⁴⁴ it delivered 1,1-cyclopropanediester **3a** in moderate enantioselectivity while improving both the yield and diastereoselectivity (Figure 1, entry 3). When switching to second-generation metal-loradical catalyst [Co(P3)] (P3 = 3,5-Di^tBu-QingPhyrin),⁵⁰ which differs from [Co(P2)] by replacing one of the two methyl groups in the chiral amides with a phenyl group for potential π -stacking interactions, it improved the enantioselectivity significantly without affecting the yield and diastereoselectivity (Figure 1, entry 4). Further improvements in both stereoselectivities and reactivity were observed by using catalyst [Co(P4)] (P4 = 3,5-Di^tBu-Xu(2'-Naph)Phyrin)¹³⁰ that bears naphthyl groups (Figure 1, entry 5), indicating the possibility of enhanced π -stacking interactions. Replacement of diazomalonate **1a** by more sterically hindered *tert*-butyl methyl diazomalonate (**1b**) afforded the corresponding 1,1-cyclopropanediester **3b** in higher yield as well as with better diastereoselectivity and enantioselectivity (Figure 1, entry 6). To our delight, when methyl phenyl diazomalonate (MPDM) (**1c**) was used as the radical precursor, the cyclopropanation of styrene by [Co(P4)] gave the corresponding 1,1-cyclopropanediester **3c** in almost quantitative yield with 96% ee and 94:6 dr (Figure 1, entry 7). Furthermore, when methyl 2-naphthyl diazomalonate (**1c**) was utilized as the substrate, the catalytic reaction led to the formation of the corresponding 1,1-cyclopropanediester **3c** in 91% yield with 95% ee and 90:10 dr (Figure 1, entry 8).

Substrate scope

Under the optimized conditions, the scope of [Co(P4)]-catalyzed asymmetric cyclopropanation with MPDM (**1c**) was investigated by using different types of alkenes as the substrates (Figure 2). Like styrene, styrene derivatives with alkyl substituents could be effectively cyclopropanated by [Co(P4)] with MPDM, affording the corresponding 1,1-cyclopropanediesters **3d–3f** in almost quantitative yields with both excellent diastereoselectivities and enantioselectivities (Figure 2, entries 1–3). The [Co(P4)]/MPDM-based system was able to cyclopropanate sterically encumbered 2-methylstyrene and 2,4-dimethylstyrene as well, forming the desired cyclopropanes **3g** and **3h** with high enantioselectivities despite in moderate yields and diastereoselectivities (Figure 2, entries 4 and 5). Styrenes substituted with both electron-donating and electron-withdrawing groups were found to be also suitable substrates for the catalytic system as demonstrated with the formation of cyclopropanes **3i–3m** (Figure 2, entries 6–10). In addition, halogenated styrenes, including those substituted with Br, Cl, and F atoms, could be catalytically transformed to the desired products **3n–3s** in high yields with excellent stereoselectivities (Figure 2, entries 11–16). It is worthy of noting that even the highly electron-deficient pentafluorostyrene could be successfully cyclopropanated to produce the desired product **3s** (Figure 2, entry 16). The absolute configurations of the newly-generated stereogenic centers in **3n** and **3q** were both established as (*S,R*) by X-ray crystallography. The Co(II)-catalyzed asymmetric cyclopropanation was shown to tolerate additional functionalities such as chloromethyl, formyl, and pinacolborane groups for the production of the functionalized cyclopropanes **3t–3v** (Figure 2, entries 17–19). Furthermore, the metalloradical system was found to be compatible with polyaromatic and heteroaromatic olefins as exemplified by the stereoselective synthesis of cyclopropane derivatives **3w–3z** and **3aa–3ab** containing naphthalene, pyrrole, pyridine, indole, benzofuran, and benzothiophene, respectively (Figure 2, entries 20–25).

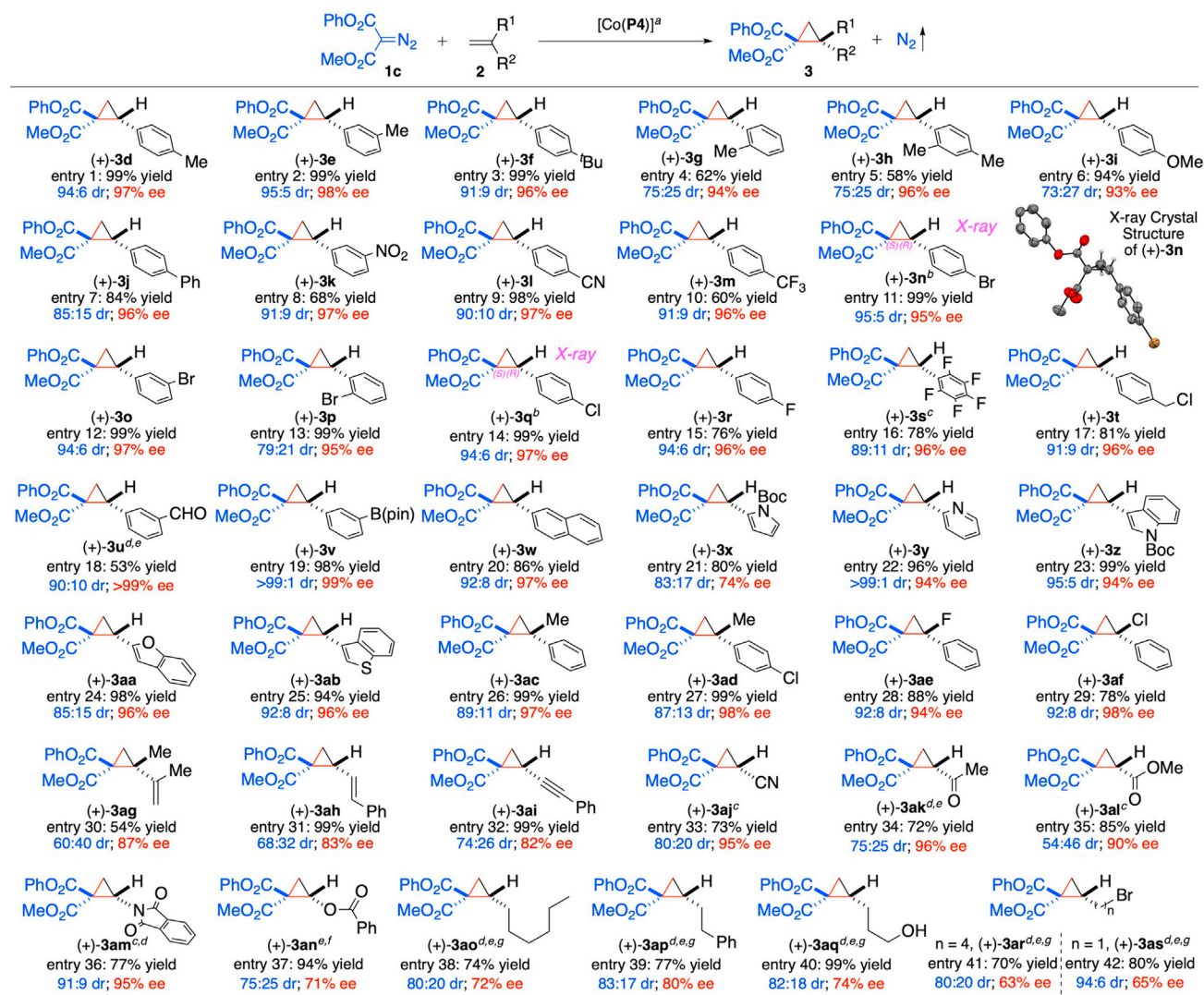


Figure 2. [Co(P4)]-catalyzed asymmetric radical cyclopropanation of alkenes with methyl phenyl diazomalonate (MPDM)

^aCarried out with diazomalonate 1c (0.10 mmol) and alkene 2 (0.12 mmol) in toluene at room temperature for 24 h in one-time fashion without slow addition using [Co(P4)] (2 mol %) under N₂; isolated yields; diastereomeric ratio (dr) determined by ¹H-NMR; enantiomeric excesses (ee) determined by chiral HPLC. ^bAbsolute configuration determined by X-ray crystallography. ^cWith 2 (0.50 mmol). ^dWith 2 (1.00 mmol). ^eUsing [Co(P4)] (5 mol %). ^fWith 2 (2.00 mmol). ^gAt 40°C.

With the use of α -substituted styrenes as the substrates, the Co(II)-based catalytic system could efficiently construct cyclopropane structures 3ac–3af with effective control of the two contiguous quaternary stereocenters (Figure 2, entries 26–29).

In addition to aromatic olefins, the [Co(P4)]/MPDM-based asymmetric system could be effectively applied to conjugated dienes and enynes, enabling chemoselective cyclopropanation of the terminal alkene units to form 2-alkenyl- and 2-alkynyl-1,1-cyclopropanediester 3ag–3ai (Figure 2, entries 30–32). Furthermore, electron-deficient alkenes, such as acrylonitrile, methyl vinyl ketone, and methyl acrylate, which are typically problematic substrates for existing catalytic systems involving electrophilic metalcarbene intermediates, could also be productively cyclopropanated with MPDM by [Co(P4)], providing the highly electrophilic multifunctionalized cyclopropanes 3aj–3al with excellent enantioselectivities albeit varied

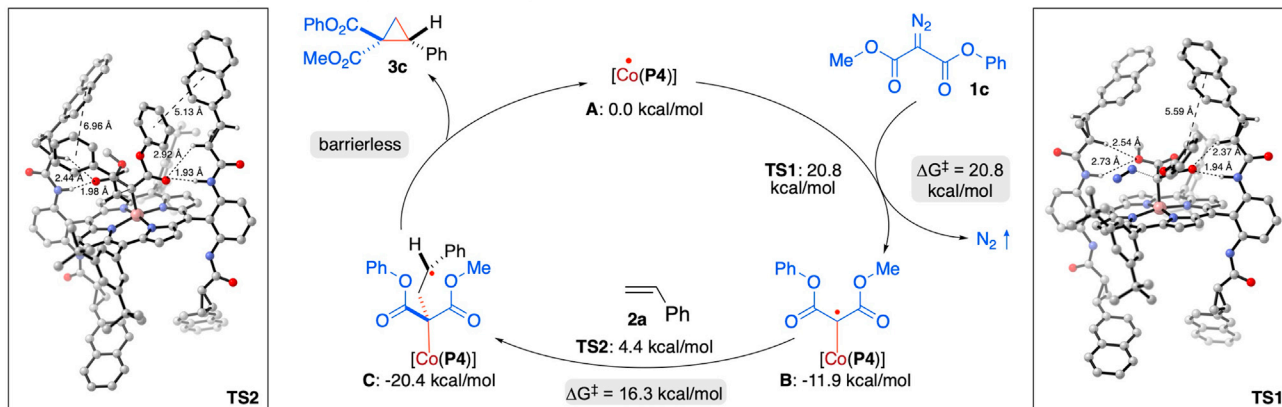
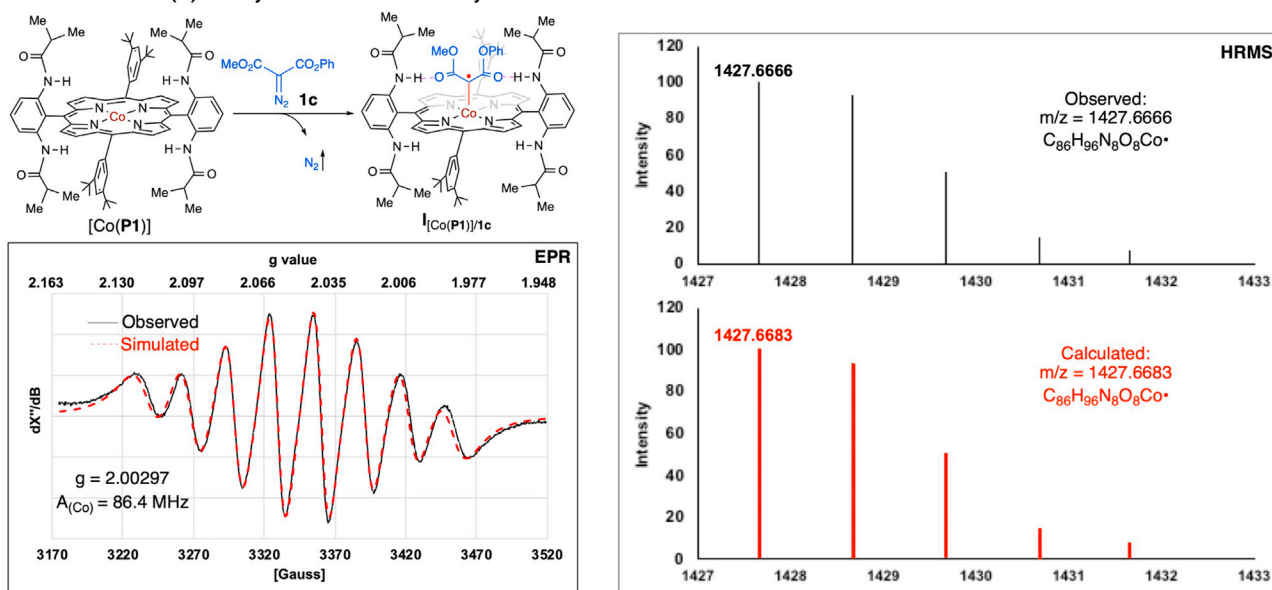
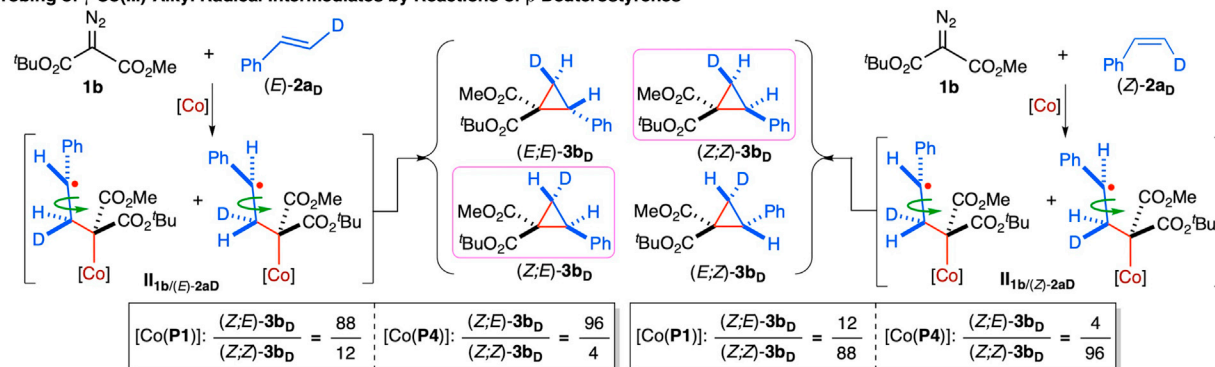
diastereoselectivities due to relatively smaller sizes compared with aromatic olefins (Figure 2, entries 33–35). Electron-rich alkenes such as *N*-vinylphthalimide and vinyl benzoate could also serve as good substrates for the asymmetric cyclopropanation, affording the corresponding donor-acceptor cyclopropanes **3am** and **3an** stereoselectively (Figure 2, entries 36 and 37). Moreover, aliphatic alkenes, which represent another class of challenging substrates for asymmetric cyclopropanation, could be cyclopropanated as well by the Co(II)-based metalloradical system as exemplified by the stereoselective formation of cyclopropanes **3ao**–**3as** in good to excellent yields (Figure 2, entries 38–42). It is worth to note the remarkable degree of functional group tolerance to the alkyl alcohol and alkyl bromide in the asymmetric formation of 1,1-cyclopropanediester **3aq**, **3ar**, and **3as** (Figure 2, entries 40–42).

Mechanistic studies

To gain insight into the proposed stepwise radical mechanism (Scheme 1), combined computational and experimental studies were conducted (Scheme 2). First, density functional theory (DFT) calculations were performed to elucidate the details of the catalytic pathway and associated energetics for the cyclopropanation reaction of styrene (**2a**) with methyl phenyl diazomalonate (**1c**) by [Co(P4)] (Scheme 2A; see supplemental information for details). The DFT calculation indicates that the formation of α -Co(III)-malonyl radical intermediate **B** upon activation of diazo **1c** by [Co(P4)] is exergonic by 11.9 kcal/mol, with the elimination of dinitrogen as the by-product. The metalloradical activation has a relatively high but accessible activation barrier (TS1: $\Delta G^\ddagger = 20.8$ kcal/mol), which represents the rate-determining step. The subsequent radical addition of radical intermediate **B** to alkene **2a**, which is exergonic by 8.5 kcal/mol, has lower activation barrier (TS2: $\Delta G^\ddagger = 16.3$ kcal/mol), leading to the formation of γ -Co(III)-benzyl radical intermediate **C**. According to the DFT calculation, the final step of 3-exo-tet cyclization through radical substitution, which is exergonic by 21.6 kcal/mol, is found to be a near barrierless process, resulting in the formation of the corresponding cyclopropane **3c** while regenerating catalyst [Co(P4)]. As illustrated with the optimized structures of transition states (Scheme 2A; see supplemental information for details), the DFT calculations also reveal the existence of multiple H-bonding and π -stacking interactions in both the transition state for the generation of intermediate α -Co(III)-malonyl radical intermediate **B** (TS1) and the transition state for its subsequent radical addition with alkene **2a** (TS2). In addition to the conformational rigidification, these noncovalent attractive interactions can cooperatively lower the activation barriers of the transition states, which may enhance catalytic reactivity and improve stereoselectivities of the product. The overall activation barrier is consistent with the fact that the catalytic reaction could proceed productively at room temperature.

In addition to DFT calculations, several experiments were carried out to detect the intermediates in this catalytic process. In an effort to directly detect α -Co(III)-malonyl radical intermediates, the isotropic electron paramagnetic resonance (EPR) spectrum was recorded at room temperature for the reaction solution of [Co(P1)] with diazomalonate **1c** in benzene in the absence of alkenes (Scheme 2B). The spectrum displayed strong signals with observed isotropic *g* value of ~ 2.00 . The well-resolved octet signals, which are diagnostic of Co(III)-supported organic radicals, indicated the formation of α -Co(III)-malonyl radical $I_{[\text{Co(P1)}/1c]}$ upon metalloradical activation of diazomalonate **1c** by [Co(P1)] with translocation of the spin from the Co(II) center to the α -C atom. The observed octet signals could be agreeably simulated on the basis of hyperfine coupling by ^{59}Co ($I = 7/2$) with *g* value of 2.00297 and $A_{(\text{Co})}$ of 86.4 MHz (see supplemental information for details). In addition, α -Co(III)-malonyl radical $I_{[\text{Co(P1)}/1c]}$ from the reaction mixture of [Co(P1)] with diazomalonate **1c** could

A DFT Calculation of Energetics of [Co(P4)]-Catalyzed Cyclopropanation

B Detection of α -Co(III)-Malonyl Radical Intermediates by EPR and HRMSC Probing of γ -Co(III)-Alkyl Radical Intermediates by Reactions of β -Deuteriostyrenes

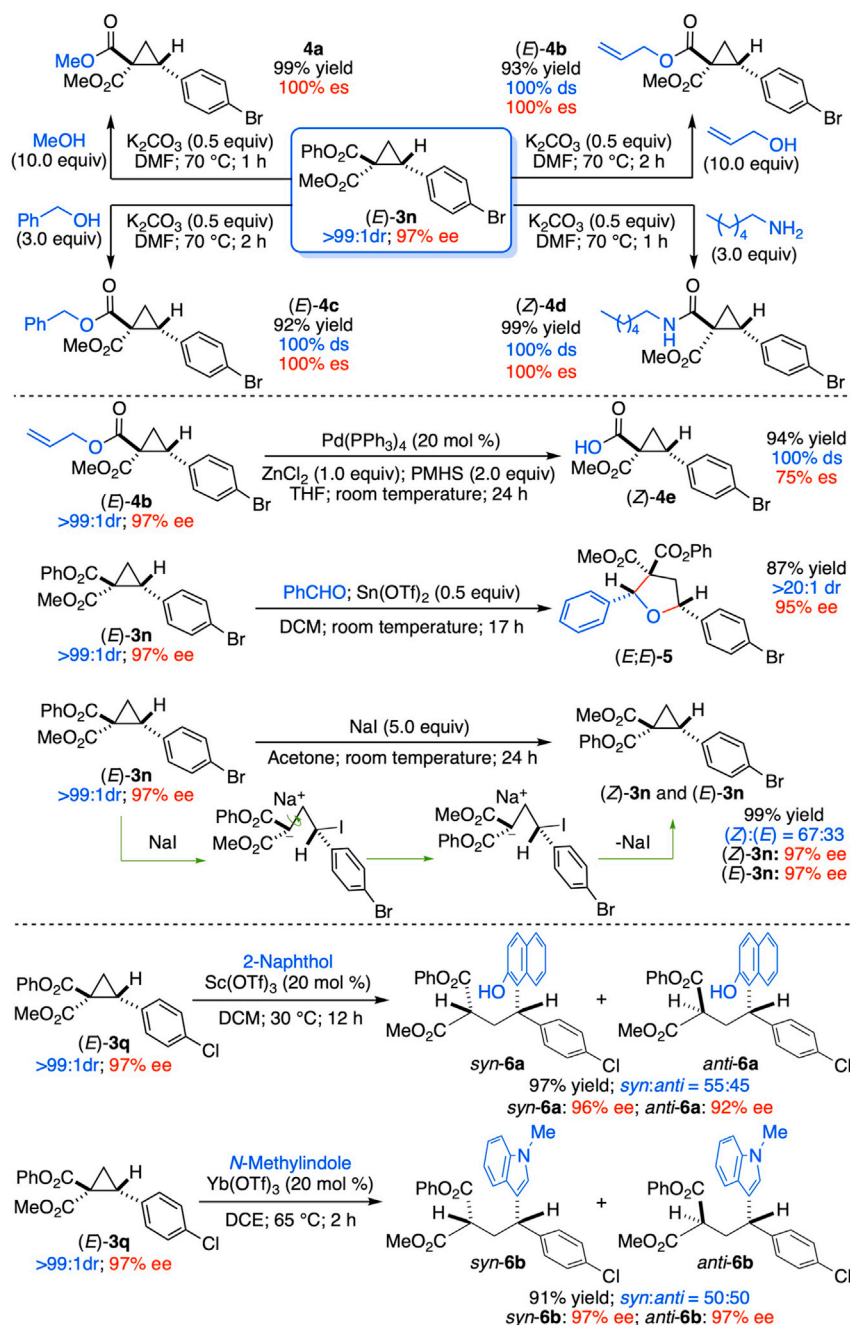
Scheme 2. Mechanistic studies for Co(II)-catalyzed olefin cyclopropanation with diazomalonates

also be detected by high-resolution mass spectrometry (HRMS) with ESI ionization in the absence of any additives as electron carriers. The obtained spectrum clearly revealed a signal corresponding to $[(P1)Co(C(CO_2CH_3)(CO_2C_6H_5))]^+$ ($m/z = 1,427.6666$), which resulted from neutral α -Co(III)-malonyl radical intermediate

$I_{[Co(P1)]/1c}$ by the loss of one electron. Both the exact mass and the pattern of isotope distribution determined by ESI-HRMS matched almost perfectly with those calculated from the formula $C_{86}H_{96}N_8O_8Co \cdot$ of $[(P1)CoC(CO_2CH_3)(CO_2C_6H_5)]^+$ (see [supplemental information](#) for details). To probe the intermediacy of γ -Co(III)-alkyl radical II associated with subsequent steps of radical addition and radical cyclization in the proposed mechanism, both (*E*)- and (*Z*)- β -deuteriostyrene ((*E*)-**2a_D** and (*Z*)-**2a_D**) were utilized as the substrates for the Co(II)-catalyzed cyclopropanation ([Scheme 2C](#)). Different from concerted mechanism that gives rise to stereospecific products, stepwise radical mechanism may generate four possible isotopomers of the cyclopropanes from the reaction of both (*E*)-**2a_D** and (*Z*)-**2a_D** due to potential rotation of the β -C–C bond in γ -Co(III)-benzyl radical intermediate II before the ring closure. To this end, unsymmetrical *tert*-butyl methyl diazomalonate (**1b**) was chosen as the radical precursor for the probing experiments because of its noticeable slower reaction rate, which was expected to provide higher probability of the β -C–C bond rotation in the corresponding γ -Co(III)-benzyl radical intermediate II. As expected, it was found that Co(II)-catalyzed cyclopropanation reactions of both (*E*)-**2a_D** and (*Z*)-**2a_D** with **1b** generated the cyclopropane product as a mixture of the four diastereomers: (*E*;*E*)-**3b_D**; (*Z*;*Z*)-**3b_D**; (*Z*;*E*)-**3b_D**; and (*E*;*Z*)-**3b_D** (see [supplemental information](#) for details). Among the four isotopomers, the ratio of (*Z*;*E*)-**3b_D** to (*Z*;*Z*)-**3b_D** could be accurately determined from analysis of the reaction mixtures by 1H - and 2H -NMR. When [Co(P4)] was used as the catalyst, cyclopropanation of (*E*)-**2a_D** with **1b** gave a 96:4 ratio of (*Z*;*E*)-**3b_D** to (*Z*;*Z*)-**3b_D**, whereas the ratio was switched to 4:96 for cyclopropanation of (*Z*)-**2a_D** with **1b**. The observation of (*Z*;*Z*)-**3b_D** from (*E*)-**2a_D** and (*Z*;*E*)-**3b_D** from (*Z*)-**2a_D** is evidently a result of the rotation of the β -C–C bond in intermediates $II_{1b/(E)-2aD}$ and $II_{1b/(Z)-2aD}$, respectively. When less sterically hindered [Co(P1)] was used as the catalyst, a significantly different isotopomeric ratio of (*Z*;*E*)-**3b_D** to (*Z*;*Z*)-**3b_D** was observed for both reactions of (*E*)-**2a_D** (from 96:4 to 88:12) and (*Z*)-**2a_D** (from 4:96 to 12:88). The observed difference in the ratio of (*Z*;*E*)-**3b_D** to (*Z*;*Z*)-**3b_D** indicates that the less-crowded ligand environment of [Co(P1)] permitted relatively more facile rotation of the β -C–C bond in the γ -Co(III)-benzyl radical intermediates $II_{1b/(E)-2aD}$ and $II_{1b/(Z)-2aD}$. Together with the direct observation of α -Co(III)-malonyl radical intermediate I by EPR and HRMS, these results provided convincing evidence to support the underlying stepwise radical mechanism for Co(II)-catalyzed olefin cyclopropanation with diazomalonates.

Synthetic applications

In view of the difference in reactivity between methyl and phenyl esters, the resulting enantioenriched (*E*)-1,1-cyclopropanediester from the Co(II)-catalyzed asymmetric cyclopropanation could be stereospecifically transformed to different chiral cyclopropane derivatives ([Scheme 3](#)). For example, the better leaving ability of the phenoxy group over the methoxy group enabled selective transesterification of phenyl ester with various alcohols, as exemplified with the transformations of 1,1-cyclopropanediester (*E*)-**3n**.¹³¹ In the presence of K_2CO_3 as the base, the unsymmetrical methyl phenyl diester (*E*)-**3n** could readily react with methanol in DMF to form the symmetrical bismethyl diester **4a** in near quantitative yield (99%) with full retention of the original high enantiopurity (100% es). Under similar conditions, methyl phenyl diester (*E*)-**3n** underwent selective transesterification reactions with allylic alcohol and benzyl alcohol as well, producing methyl allyl diester (*E*)-**4b** and methyl benzyl diester (*E*)-**4c**, respectively, in high yields (93% and 92%) with full retention of the original high (*E*)-diastereomeric purity (100% ds) as well as enantiopurity (100% es). In addition to transesterification, (*E*)-**3n** could proceed selective amidation, as demonstrated with the stereospecific formation of 1,1-cyclopropaneesteramide (*Z*)-**4d** in near quantitative yield (99%) without diminishing the original high



Scheme 3. Chemical transformations of optically active chiral 1,1-cyclopropanediester

diastereomeric purity (100% ds) and enantiopurity (100% es) when reacting with N-hexylamine under the similar conditions.

Besides the transesterification and amidation reactions, the resulting enantioenriched 1,1-cyclopropanediester from the catalytic process could be transformed to other interesting compounds (Scheme 3). For example, the allylic group in the transesterification product (E)-4b was effectively removed by a Pd-catalyzed hydrogenation reaction, producing the corresponding 1,1-cyclopropaneester carboxylic acid (Z)-4e in high yield (94%) with retention of the original diastereomeric purity

(100% ds) but some loss of the optical purity (75% es).¹³² As the donor-acceptor type of cyclopropanes, the resulting enantioenriched 1,1-cyclopropanediester could function as effective 1,3-dipoles to undergo [3 + 2] cycloaddition as shown by the 1,3-dipolar cycloaddition of 1,1-cyclopropanediester (*E*)-**3n** with benzaldehyde under the catalysis of Sn(OTf)₂, affording multi-substituted tetrahydrofuran (*E*;*E*)-**5** containing three stereocenters in high yield (87%) with excellent diastereoselectivity (>20:1 dr) and high enantioselectivity (95% ee).^{90,102,103,105,133–151} While (*E*)-diastereomers were produced as the major diastereomers in [Co(P4)]-catalyzed olefin cyclopropanation with MPDM, the (*Z*)-diastereomers could be generated through an iodide-mediated stereospecific conversion. For example, when (*E*)-**3n** was treated with NaI (5.0 equiv) at room temperature, it resulted in the conversion to (*Z*)-**3n** as the major diastereomer with no loss of the original optical purity (97% ee). In addition, the three-membered ring structure in the enantioenriched 1,1-cyclopropanediester could be stereoselectively opened with common nucleophiles¹⁵² as exemplified by effective ring-opening reaction of 1,1-cyclopropanediester (*E*)-**3q** with 2-naphthol in the presence of Sc(OTf)₃,⁸⁵ affording chiral acyclic diester **6a** in excellent yield (97%) as a mixture of diastereomers (*syn:anti* = 55:45) without significant erosion of the high optical purities for both *syn*-diastereomers (96% ee) and *anti*-diastereomers (92% ee). As another example, 1,1-cyclopropanediester (*E*)-**3q** could also undergo facile ring-opening reaction with *N*-methylindole in the presence of Yb(OTf)₃,¹⁵³ leading to the formation of chiral acyclic diester **6b** in high yield (91% yield) as a mixture of diastereomer (*syn:anti* = 50:50) with the complete preservation of the original optical purity for both *syn*-diastereomers (97% ee) and *anti*-diastereomers (97% ee). Presumably, the acidity of the tertiary α-C–H bond at the second stereogenic center bearing two ester groups is responsible for the generation of both *syn*- and *anti*-diastereomers as a mixture in products **6a** and **6b**.

Conclusions

In summary, we have developed the first catalytic system via Co(II)-based MRC that is highly effective for asymmetric cyclopropanation of alkenes with MPDM, a common unsymmetrical diazomalonate. With *D*₂-symmetric chiral amidoporphyrin 3,5-Di^tBu-Xu(2'-Naph)Phyrin as the supporting ligand, the Co(II)-based metalloradical system can smoothly activate MPDM even at room temperature with effective differentiation of the two ester groups to different cyclopropanate alkenes, affording 1,1-cyclopropanediester bearing two contiguous stereogenic centers in high yields with an excellent level of control in both diastereoselectivity and enantioselectivity. In addition to the operational simplicity and mild conditions, the Co(II)-catalyzed asymmetric cyclopropanation has been demonstrated with an unusually broad scope of alkenes and a remarkable degree of functional group tolerance. Combined computational and experimental studies provide convincing evidences in supporting the underlying stepwise radical pathway for the Co(II)-catalyzed process. The resulting enantioenriched (*E*)-1,1-cyclopropanediester from this catalytic radical process, as showcased in a number of stereospecific transformations, should find useful synthetic applications.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in [supplemental information](#).

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, X. Peter Zhang (peter.zhang@bc.edu).

Materials availability

Unique and stable reagents generated in this study will be made available on request, but we might require a payment and/or a completed materials transfer agreement if there is potential for commercial application.

Data and code availability

The crystal structure data of compounds (1*S*,2*R*)-**3n** and (1*S*,2*R*)-**3q** have been deposited in the Cambridge structural database under reference numbers CCDC 2083325 and CCDC 2097074, respectively.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.checat.2021.11.018>.

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AUTHOR CONTRIBUTIONS

J.W. conducted the experiments. J.X. and W.-C.C.L. assisted the experiments. J.X. and D.-S.W. performed DFT calculations. X.P.Z. conceived the work and directed the project. J.W. and X.P.Z. designed the experiments. J.W., J.X., and X.P.Z. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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