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Metalloradical Activation of In Situ-Generated α-Alkynyldiazomethanes for Asymmetric Radical Cyclopropanation of Alkenes

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Abstract

α-Alkynyldiazomethanes, generated in situ from the corresponding sulfonyl hydrazones in the presence of a base, can serve as effective metalloradicophiles in Co(II)-based metalloradical catalysis (MRC) for asymmetric cyclopropanation of alkenes. With D_2-symmetric chiral amidoporphyrin 2,6-DiMeO-QingPhyrin as the optimal supporting ligand, the Co(II)-based metalloradical system can efficiently activate different α-alkynyldiazomethanes at room

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Experimental details and analytical data for all new compounds (PDF)

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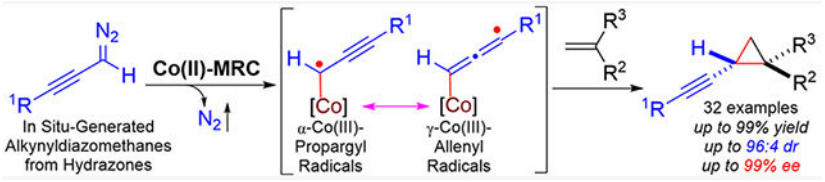
temperature for highly asymmetric cyclopropanation of a broad range of alkenes. This catalytic radical process provides a general synthetic tool for stereoselective construction of alkynyl cyclopropanes in high yields with high both diastereoselectivity and enantioselectivity. Combined computational and experimental studies offer several lines of evidence in support of the underlying stepwise radical mechanism for the Co(II)-catalyzed olefin cyclopropanation involving a unique α-metalloradical intermediate that is associated with two resonance forms of α-Co(III)-propargyl radical and γ-Co(III)-allenyl radical. The resulting enantioenriched alkynyl cyclopropanes, as showcased with several stereospecific transformations, may serve as valuable chiral building blocks for stereoselective organic synthesis.

Graphical Abstract



INTRODUCTION

Radical reactions have been increasingly exploited as complementary synthetic methods to ionic reactions in modern organic synthesis as they enjoy intrinsic attributes such as high reactivity and tolerance of functional groups.[1] Among significant challenges facing this endeavor is the control of reactivity as well as selectivities in the reactions of free organic radicals, especially enantioselectivity.[2] Rising to these challenges, metalloradical catalysis (MRC) has emerged as a conceptually new approach to the development of stereoselective radical reactions through catalytic generation of metal-supported organic radicals as key catalytic intermediates.[3–5] As stable 15e-metalloradicals with well-defined low-spin d^7-configuration, Co(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] have been recognized as a family of open-shell catalysts that are effective for asymmetric cyclopropanation of alkenes with diazo compounds.[6] During the Co(II)-catalyzed cyclopropanation, the initially generated α-metalloalkyl radical intermediates from metalloradical activation of diazo compounds, which are centrally situated inside the pocketlike environment of the chiral porphyrin ligands,[7] can be precisely governed to perform a sequence of homolytic reactions such as radical addition and radical substitution with olefin substrates, leading to productive formation of cyclopropanes with effective control of diastereoselectivity and enantioselectivity. Except for a few recent examples of using α-aryldiazomethanes,[8] Co(II)-based radical cyclopropanation has so far been mostly involved with the use of acceptor- and acceptor/acceptor-substituted diazo compounds as metalloradicophiles.[6] In all the previous cases, the key α-Co(III)-supported C-centered radical intermediates are stabilized by C(sp^2)-based carbonyl or aryl substituents through potential H-bonding interactions with the amide units of the catalyst, facilitating the reactivity and stereoselectivity of the catalytic radical process. It was unclear if Co(II)-based metalloradical system could also be applicable to other types of diazo compounds with substituents beyond C(sp^2)-based carbonyl and aryl groups. Specifically, we were intrigued

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to learn whether α-alkynyldiazomethanes, a common type of diazo compounds containing C(sp)-based alkynyl substituents, could be employed as potential metalloradicophiles by Co(II)-based metalloradical system for radical olefin cyclopropanation (Scheme 1). As α-alkynyldiazomethanes **1′** are typically generated in situ from corresponding hydrazones **1** under basic conditions,[9] it would be crucially important to match the rates between the diazomethane generation and the ensuing metalloradical activation in order to preclude their thermal decomposition to form pyrazole and azine side products. Apart from the concern with the effectiveness for initially generated α-Co(III)-propargyl radicals **I** to the olefin substrates to control the enantioselectivity for the first C–C bond formation? What also under question is the control of chemoselectivity as well as the diastereoselectivity during the final step of radical substitution of γ-Co(III)-alkyl radicals **II** for the second C—C bond formation. Considering the presence of the C≡C triple bond, could γ-Co(III)-alkyl radicals **II** undergo the desired 3-*exo-tet* radical cyclization chemoselectively over the potentially competitive 4-*exo-dig* and 5-*endo-dig* cyclization, leading to diastereoselective construction of cyclopropanes? We hoped to address these and related issues through judicious development of Co(II)-based metalloradical catalyst by fine-tuning the environments of D_2-symmetric chiral amidoporphyrin ligand. If implemented successfully, then it would lead to the development of a new catalytic radical process for asymmetric olefin cyclopropanation with in situ-generated α-alkynyldiazomethanes to construct chiral alkynyl cyclopropanes. In addition to serving as useful intermediates for stereoselective organic synthesis, chiral alkynyl cyclopropanes occur as common substructures in many important natural products and drug molecules (see Figure S1).[11]

Metal-catalyzed asymmetric cyclopropanation of alkenes with α-alkynyldiazomethanes offers a potentially general approach for stereoselective construction of valuable chiral alkynyl cyclopropanes.[12–14] While donor/acceptor-substituted diazo compounds alkynyldiazoacetates were successfully metalloradical activation of α-alkynyldiazomethanes **1'**, the additional issue of regioselectivity could arise from two potential reactivity modes of the resulting α-metalloalkyl radical intermediates that are associated with the two resonance forms of α-Co(III)-propargyl radicals **I** and γ-Co(III)-allenyl radicals **I'**.[10] Furthermore, in the absence of the aforementioned H-bonding interactions, what elements could be utilized during the subsequent radical addition of the employed by Davies and co-workers as carbene precursors for Rh_2-catalyzed asymmetric cyclopropanation,[15] donor-substituted diazo compounds α-alkynyldiazomethanes, in contrast, have been scarcely explored.[16] A single example of cyclopropanation of *trans*-stilbene with the use of α-alkynyldiazomethane could be found in a recent report by Bi and co-workers on Ag-based catalytic system involving in situ generation of diazo compounds from *N*-nosylhydrazones.[16c] This underdevelopment is mainly attributed to the inherent propensity of α-alkynyldiazomethanes toward the formation of the stable aromatic pyrazoles.[17] To circumvent the problem, Echavarren and co-workers recently reported an innovative two-step approach for synthesis of alkynyl cyclopropanes from alkenes based on Rh_2-catalyzed decarbenation of 7-alkynyl cycloheptatrienes as alkynylcarbene precursors.[18] To the best of our knowledge, there has been no previous report on catalytic system for asymmetric olefin cyclopropanation with α-alkynyldiazomethanes for stereoselective synthesis of chiral alkynyl cyclopropanes. As a new application of Co(II)-based metalloradical catalysis

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(MRC), we herein report the development of the first asymmetric catalytic system for olefin cyclopropanation that can effectively utilize α-alkynyldiazomethanes through in situ generation from the corresponding sulfonyl hydrazones in the presence of base. Through identification of an optimal D_2-symmetric chiral amidoporphyrin (D_2-Por*) as the supporting ligand, the Co(II)-based catalytic system is capable of efficiently activating different alkynyldiazomethanes at room temperature to cyclopropanate a wide range of alkenes with varied electronic and steric properties, delivering alkynyl cyclopropanes in high yields with excellent control of both diastereoselectivity and enantioselectivity. We show the importance of catalyst development through fine-tuning of the ligand environment in achieving high reactivity as well as stereoselectivities. We present combined computational and experimental studies that shed light on the underlying stepwise radical mechanism of the Co(II)-catalyzed cyclopropanation. To demonstrate the synthetic applications of the new catalytic system, we showcase several examples of stereoselective transformations of the resulting enantioenriched alkynyl cyclopropanes.

RESULTS AND DISCUSSION

Catalyst Development.

At the outset of the project, α-(phenylethynyl)diazomethane (**1a′**), which was in situ generated from corresponding trisylhydrazone **1a** in the presence of KH, was designated as the representative α-alkynyldiazomethane for asymmetric radical cyclopropanation of styrene (**2a**) using Co(II)-based metalloradical catalysts [Co(Por)] (Scheme 2; see Table S1). It was found that simple achiral metalloradical catalyst [Co(**P1**)] (**P1** = tetraphenylporphyrin) could activate the diazo compound to cyclopropanate styrene, giving desired alkynyl cyclopropane **3a** in low yield (36%) with inferior control of diastereoselectivity (14% de). With the employment of the Co(II) complex of D_{2h}-symmetric achiral amidoporphyrin [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-IbuPhyrin) as the catalyst,[19] the catalytic cyclopropanation reaction was significantly enhanced, forming cyclopropane **3a** in a higher yield (84%) with improved diastereoselectivity (56% de) in favor of the *trans*-isomer. To evaluate the feasibility of asymmetric induction during the catalytic process, Co(II) complexes of D_2-symmetric chiral amidoporphyrins were employed as the catalysts. When first-generation chiral metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-ChenPhyrin)[6a] was used, the catalytic reaction produced cyclopropane **3a** in an almost quantitative yield (98%) with the same level of diastereoselectivity (58% de) while exhibiting significant enantioselectivity (53% ee). To improve the stereoselectivities of the catalytic process, we then applied metalloradical catalyst [Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-ZhuPhyrin),[20] which is devised to achieve conformational rigidity through unique intramolecular H-bonding interactions in (*S*)-(−)-2-tetrahydrofurancarboxamide units. As expected, the catalytic reaction by [Co(**P4**)] brought about improved enantioselectivity (59% ee) but reduced diastereoselectivity (52% de) and significantly decreased yield (34%) as a result of the more sterically encumbered ligand environment. These results prompted us to explore second-generation chiral metalloradical catalysts bearing cyclopropanecarboxyamides with two contiguous stereogenic centers in the hope of further enhancing the asymmetric induction of the catalytic process. Gratifyingly, when [Co(**P5**)] (**P5** = 3,5-Di^{t}Bu-QingPhyrin) was used as the catalyst for the reaction,[6g] cyclopropane **3a**

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was produced in high yield (80%) with excellent enantioselectivity (94% ee) albeit with low diastereoselectivity (20% de). Inspired by this positive outcome, we then employed the analogous catalyst [Co(**P6**)] (**P6** = 2,6-DiMeO-QingPhyrin) bearing the same chiral amide units but with different achiral *meso*-aryl groups to further enhance the rigidity of the chiral environment. To our delight, the catalytic reaction by [Co(**P6**)] indeed significantly improved both diastereoselectivity (74% de) and yield (90%) while maintaining the excellent enantioselectivity (96% ee). The remarkable difference in performance among the metalloradical catalysts indicates that subtle alteration in ligand environment can give rise to significant improvement in catalytic reactivity as well as stereoselectivities, manifesting the effectiveness of catalyst development in controlling the radical process.

Substrate Scope.

Under the optimized conditions, the scope and versatility of [Co(**P6**)]-catalyzed asymmetric cyclopropanation were evaluated using different α-alkynyldiazomethanes through in situ generation from the corresponding sulfonyl hydrazones **1** under the basic condition with various olefins (Table 1). Similar to α-alkynyldiazomethane **1a**', α-(arylethynyl)diazomethanes bearing substituents with varied electronic and steric properties on the phenyl group could be effectively employed as metalloradicophiles for the Co(II)-based catalytic system as shown for asymmetric cyclopropanation of styrene (**2a**) as the representative olefin substrate. For example, α-(arylethynyl)diazomethanes bearing alkyl substituents at different aryl positions such as *p*-Me and *o*-iPr could be efficiently activated by [Co(**P6**)] at room temperature to cyclopropanate styrene, producing desired alkynyl cyclopropanes **3b** and **3c** in high yields with good diastereoselectivities and excellent enantioselectivities (entries 1 and 2). Furthermore, [Co(**P6**)] could activate α-(arylethynyl)diazomethanes containing an electron-donating–OMe group at all the three different positions of the aryl group for the cyclopropanation reaction, allowing stereoselective construction of corresponding alkynyl cyclopropanes **3d**—**3f** in high yields with high diastereoselectivities and excellent enantioselectivities (entries 3—5). It is interesting to note that the observed diastereoselectivity increases when the position of MeO-substituent in cyclopropanes **3d**—**3f** moves from *para*- to the *meta*- to the *ortho*-position. Likewise, α-(arylethynyl)diazomethanes bearing electron-withdrawing groups could also be suitable metalloradicophiles as exemplified by asymmetric synthesis of alkynyl cyclopropanes **3g** and **3h** in high yields with excellent control of stereoselectivities (entries 6 and 7). Moreover, naphthalenecontaining α-alkynyldiazomethanes could also be effectively activated by [Co(**P6**)] under the same conditions for asymmetric cyclopropanation reaction, leading to high-yielding formation of corresponding alkynyl cyclopropane **3i** with both high diastereoselectivity and enantioselectivity (entry 8). In addition to α-(arylethynyl)diazomethanes, the Co(II)-based metalloradical system was shown to be applicable to α-alkynyldiazomethanes containing certain nonaryl substituents as demonstrated by catalytic asymmetric cyclopropanation of styrene with alkyl substituted diazo derivative, generating desired cyclopropane **3j** with high stereoselectivities albeit in moderate yield (entry 9). Moreover, a triisopropylsilyl (TIPS)-substituted diazo derivative can also serve as suitable substrate, furnishing the corresponding cyclopropane **3k** in good yield with high diastereoselectivity and enantioselectivity (entry 10).

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In addition to being capable of using different α-alkynyldiazomethanes, the Co(II)-based system for asymmetric cyclopropanation was found to be suitable to a wide range of alkenes under the optimized conditions (Table 1). Like styrene, its derivatives bearing various substituents such as –*tert*-Bu, –OMe, –CN, and $-NO_2$ groups at different positions could be reliably cyclopropanated by [Co(**P6**)] with α-alkynyldiazomethane **1a**', generating corresponding alkynyl cyclopropanes **3l**–**3o** in similarly high yields with effective control of diastereoselectivities and enantioselectivities (entries 11–14). Additionally, halogenated aromatic olefins could also serve as suitable substrates in [Co(**P6**)]-catalyzed asymmetric cyclopropanation as exemplified by highly stereoselective generation of alkynyl cyclopropanes **3p**–**3s** with halogen atoms at various positions (entries 15–18). Furthermore, extended aromatic olefins like 2-vinylnaphthalene could be also effectively applied to the catalytic system, affording alkynyl cyclopropane **3t** in excellent yield with high diastereoselectivity and outstanding enantioselectivity (entry 19). Moreover, the Co(II)-based cyclopropanation was shown to be compatible with heteroaryl alkenes such as those containing thiophene, pyridine, and benzothiophene, affording corresponding heteroaryl cyclopropanes **3u**–**3w** in high yields with high stereoselectivities (entries 20–22). To further highlight the unique feature of Co(II)-based metalloradical catalysis, even electron-deficient olefins such as acrylamide and ethyl acrylate, which are challenging substrates for catalytic cyclopropanation systems involving electrophilic metallocarbene intermediates, could be effectively cyclopropanated by [Co(**P6**)] to form desired products **3x** and **3y** in high yields with high stereoselectivities (entries 23 and 24). In addition to monosubstituted olefins, 1,1-disubstituted olefins like α-methylstyrene and α-bromostyrene could serve as suitable substrates as well, allowing for highly stereoselective construction of trisubstituted cyclopropanes **3z** and **3aa** with excellent control of the newly generated quaternary carbon stereogenic centers (entries 25 and 26). The absolute configuration of the major enantiomer of alkynyl cyclopropane **3aa** was established as (*S,S*) by X-ray crystallography. When conjugated dienes and enynes were used as the substrates, [Co(**P6**)] could regio- and chemoselectively cyclopropanate the terminal double bonds, leading to exclusive formation of cyclopropanes **3ab**–**3ad** in high yields with high stereoselectivities without affecting the internal alkene and alkyne units (entries 27–29). It is interesting to note the C_2-symmetric structure of bisalkynyl cyclopropane **3ad**. Notably, [Co(**P6**)]-based catalytic system proved to be even effective for asymmetric cyclopropanation of unactivated alkyl-substituted olefins, affording alkynylcyclopropanes **3ae** and **3af** in moderate yields with high stereoselectivities (entries 30 and 31).

Mechanistic Studies.

Combined computational and experimental studies were carried out to shed light on the underlying stepwise radical mechanism of Co(II)-based catalytic system for asymmetric cyclopropanation (Scheme 3). First, density functional theory (DFT) calculations were conducted to examine the details of the catalytic pathway and associated energetics for asymmetric cyclopropanation of styrene (**2a**) with (phenylethynyl)diazomethane (**1a**') by metalloradical catalyst [Co(**P6**)] (**A**) (Scheme 3A; see the Supporting Information for details). The DFT calculations reveal the initial formation of intermediate **B** resulting from the binding of diazomethane **1a**' by catalyst [Co(**P6**)] through a network of noncovalent attractive interactions, including H-bonding and π-stacking interactions, as illustrated in the

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DFT-optimized structure (Scheme 3A). The binding event, which is slightly exergonic by 1.2 kcal/mol, positions the α-carbon atom of **1a**' in close proximity to the Co(II)-metalloradical center of [Co(**P6**)] (C···Co: ~2.792 Å) for the subsequent activation. Bound diazomethane **1a**' is then further activated by catalyst [Co(**P6**)] to generate α-Co(III)-propargyl radical intermediate **C** with the release of dinitrogen as byproduct. The metalloradical activation, which is exergonic by 18.2 kcal/mol, is found to be the rate-determining step associated with a relatively high but accessible activation barrier ($\Delta G^{\ddagger}_{TS1}$ = 16.3 kcal/mol). As displayed by the spin plot of intermediate **C** (Scheme 3A), the spin density mainly distributes on α- and γ-carbon atoms in similar amounts (α-C: 0.59; γ-C: 0.41), which can be represented as two resonance forms of α-Co(III)-propargyl radical **C** and γ-Co(III)-allenyl radical **C**'. To rationalize the observed regioselectivity of the catalytic reaction, we calculated the energetics associated with subsequent radical addition to alkene **2a** by both α-Co(III)-propargyl radical form **C** and γ-Co(III)-allenyl radical form **C**', leading to the formation of γ-Co(III)-benzyl radical intermediate **D** and ε-Co(III)-benzyl radical intermediate **D**', respectively. DFT calculations indicate radical addition of propargyl radical **C** is more favorable than allenyl radical **C**' both kinetically ($\Delta G^{\ddagger}_{TS2}$ = 11.4 kcal/mol; $\Delta G^{\ddagger}_{TS2'}$ = 18.7 kcal/mol) and thermodynamically ΔG°_{D} = −11.1 kcal/mol; $\Delta G^{\circ}_{D'}$ = −7.2 kcal/mol). According to the DFT calculations, γ-Co(III)-alkyl radical **D** then undergoes radical substitution to produce alkynyl cyclopropane **3a** while regenerating metalloradical catalyst [Co(**P6**)]. This final step of 3-*exo*-*tet* radical cyclization, which is exergonic by 15.2 kcal/mol, is found to be an almost barrierless process. The overall low activation barrier is in accordance with the experimental observation that the catalytic reaction could proceed effectively even at room temperature.

To provide direct evidence for the existence of the key α-Co(III)-propargyl radical intermediate, efforts were made to trap the Co-supported organic radicals for experimental detection and characterization. First, the spin trapping reagent *N*-*tert*-butyl-α-phenylnitrone (PBN) was added to the reaction mixture of alkynyldiazomethane **1f**' with metalloradical catalyst [Co(**P1**)] in the absence of olefin substrate and was then monitored by X-band electron paramagnetic resonance (EPR) spectroscopy at room temperature (Scheme 3B; see the Supporting Information for details). The observed isotropic EPR spectrum exhibits strong signals with the characteristic splitting pattern at g-value of ~2.00, which was taken as the evidence for formation of radical $\mathbf{III}_{[Co(\mathbf{P1})]/\mathbf{1f}}$ resulting from PBN trapping of the initially generated Co(III)-propargyl radical intermediate $\mathbf{I}_{[Co(\mathbf{P1})]/\mathbf{1f}}$.[21] In accordance with the spin density distribution from DFT calculations (Scheme 3A), the observed broad spectrum (in black) could be near perfectly simulated (in red) as four well-defined triplet of doublet signals (Scheme 3B) by involving four isomeric PBN-trapped radical species that are originated from the two resonance forms of α-Co(III)-propargyl radical intermediate $\mathbf{I}_{[Co(\mathbf{P1})]/\mathbf{1f}}$ and γ-Co(III)-allenyl radical intermediate $\mathbf{I}'_{[Co(\mathbf{P1})]/\mathbf{1f}}$ on the basis of the hyperfine coupling by ^{14}N (I = 1) and ^{1}H (I = 1/2): 81% of O-centered radicals $\mathbf{III}_{[co(\mathbf{P1})]/\mathbf{1f}}$ from $\mathbf{I}_{[Co(\mathbf{P1})]/\mathbf{1f}}$ as two diastereomers (59% of major diastereomer: g = 2.00627, $A_{(N)}$ = 41.9 MHz, $A_{(H)}$ = 9.5 MHz; 22% of minor diastereomer: g = 2.00652, $A_{(N)}$ = 38.7 MHz, $A_{(H)}$ = 8.5 MHz) and 19% of O-centered radicals $\mathbf{III}'_{[co(\mathbf{P1})]/\mathbf{1f}}$ from $\mathbf{I}'_{[Co(\mathbf{P1})]/\mathbf{1f}}$ as two diastereomers (12% of major isomer: g = 2.00622, $A_{(N)}$ = 40.5 MHz, $A_{(H)}$ = 6.2 MHz; 7% of minor isomer: g = 2.00636, $A_{(N)}$ = 38.9 MHz, $A_{(H)}$ = 6.0 MHz).

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Besides the spectroscopic observation of the key radical intermediate by EPR, significant efforts were devoted to directly trap α-Co(III)-propargyl radical intermediate by stable TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) radical for structural characterization (Scheme 3c). When the metalloradical activation of alkynyldiazomethane **1f'** by [Co(**P1**)] was conducted in the presence of TEMPO without alkene substrates, we were able to isolate product **4f** in 40% yield, which was shown to contain two geminal TEMPO units at the propargylic position. Formation of bis-TEMPO-trapped product **4f** evidently implies the initial generation of α-Co(III)-propargyl radical $\mathbf{I}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{1f}}$, which was trapped by TEMPO through radical recombination to generate intermediate $\mathbf{IV}[_{\mathrm{Co}}(_{\mathrm{P1}})]/_{1\mathrm{f}}$. Subsequent radical substitution reaction of $\mathbf{IV}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{1f}}$ with a second molecule of TEMPO was likely responsible for the final formation of bis-TEMPO-trapped product **4f** upon the homolytic cleavage of the weak Co(III)–C bond. Analogous TEMPO-trapping experiment was carried out with alkynyldiazomethane **1g,** resulting in the isolation of bis-TEMPO-trapped product **4g** in 46% yield, the structure of which was further confirmed by the X-ray crystallography (Scheme 3C). In both reactions, α,α-bis-TEMPO-trapped products were exclusively generated from α-Co(III)-propargyl radical intermediate without the formation of α,γ-bis-TEMPO-trapped products from its γ-Co(III)-allenyl radical resonance form. The observed preference of reactivity at α-propargyl position over γ-allenyl position is in good accordance with the regioselectivity of Co(II)-based catalytic system for asymmetric cyclopropanation, which is also supported by the DFT computational studies.

Synthetic Applications.

Considering that the resulting enantioenriched alkynyl cyclopropanes contain both versatile C≡C triple bond as well as relatively acidic tertiary C—H bonds on the cyclopropane ring, they may serve as useful intermediates for stereoselective organic synthesis. To this end, we carried out several stereoselective transformations using enantioenriched alkynyl cyclopropanes **3f** (95% ee) and **3a** (96% ee) as the model compounds to demonstrate the synthetic utility of this methodology (Scheme 4).[22] For example, it was shown that enantioenriched alkynyl cyclopropane **3f** could undergo effective *cis*-hydrogenation with dihydrogen in the presence of Lindlar catalyst, generating vinyl cyclopropane **5f** with (*Z*)-configuration exclusively in almost quantitative yield (99% yield) without any erosion of the original diastereoselectivity (100% ds) and enantioselectivity (100% es) (Scheme 4A). Furthermore, by taking advantage of the difference in acidity between the two tertiary C—H bonds on the cyclopropane ring, we demonstrated that the C—H bond neighboring at the alkynyl substituent in cyclopropane **3f** could be preferentially deprotonated with *n*-BuLi over the C—H bond neighboring at the aryl substituent, leading to site-selective generation of cyclopropyl lithium intermediate **3f·Li** (Scheme 4B).[22a] By adding different alkyl halides as the electrophiles, the in situ-generated cyclopropyl lithium intermediate **3f·Li** could undergo subsequent nucleophilic substitution reactions, allowing for stereoselective synthesis of trisubstituted cyclopropanes with three different types of groups while creating an all-carbon quaternary stereogenic center without the formation of the potential allenylic products. For instance, the in situ reaction of **3f·Li** with methyl iodide furnished corresponding 1-methyl-1-alkynyl-2-phenyl cyclopropane **6f** in moderate yield (66%) with notable loss of stereopurities (50% ds and 85% es) presumably due to the small size of the electrophile (Scheme 4B). When the larger benzyl bromide was added

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as the electrophile, the reaction could deliver corresponding 1-benzyl-1-alkynyl-2-phenyl cyclopropane **7f** in higher yield (72%) with complete retention of the diastereopurity (100% ds) and without significant loss of the original enantiopurity (98% es) (Scheme 4C). The reaction also worked similarly well with allylic bromide as the electrophilic partner, affording desired 1-allyl-1-alkynyl-2-phenyl cyclopropane **8f** in high yield (92%) while maintaining the majority of the stereopurities (93% ds and 88% es) (Scheme 4D). Moreover, oxidative click reaction of cyclopropane **3f** with sodium azide could be successfully achieved in the presence of $PhI(OAc)_2$, producing 1,2,3-triazole-substituted cyclopropane **9f** in high yield (81%) without any erosion of the original diastereoselectivity (100% ds) and enantioselectivity (100% es) (Scheme 4E).[22b] Presumably, the in situ-generated azidyl radical first underwent radical addition with the C≡ bond in cyclopropane **3f** to generate vinyl radical intermediate **A.** Ensuing 5-*endo-dig* radical cyclization of intermediate **A** caused the formation of 5-membered aminyl radical intermediate **B,** which gave rise to final product **9f** after hydrogen atom abstraction from the solvent.[22b] In addition to these demonstrated transformations for stereoselective synthesis of new cyclopropane derivatives, the three-membered cyclopropane ring in the resulting enantioenriched alkynyl cyclopropanes could be expanded to form 5-membered cyclic structure as exemplified by the reaction of enantioenriched alkynyl cyclopropane **3a** with $Na_2S{\cdot}9H_2O$ in DMA at high temperature, affording 2-benzylidenetetrahydrothiophene **4a** in high yield (73%) with good configuration control of the trisubstituted olefin (*Z:E* = 85:15) but with only moderate enantioselectivity (36% ee) (Scheme 4F). According to the proposed mechanism,[22c] the cyclopropane ring in **3a** was first opened by in situ-generated trisulfur radical anion $S_3^{\bullet-}$ via radical substitution to generate propargylic radical intermediate **C**, which was protonated by H_2O after one-electron reduction and followed by homolysis of the S—S bond to form thiyl radical intermediate **D** while releasing disulfur radical anion $S_2^{\bullet-}$. The following 5-*exo-dig* radical cyclization of intermediate **D** led to the formation of vinyl radical intermediate **E**, which went through another sequence of reduction and protonation to give final product **4a**.[22c]

CONCLUSIONS

In summary, we have developed the first asymmetric catalytic system that can use in situ-generated α-alkynyldiazomethanes for direct cyclopropanation of alkenes via Co(II)-based metalloradical catalysis (MRC). On the basis of a remarkable ligand effect on the Co(II)-based catalytic system, D_2-symmetric chiral amidoporphyrin 2,6-DiMeO-QingPhyrin has been identified as the optimal supporting ligand that offers suitable steric, electronic, and chiral environments surrounding the Co(II)-metalloradical center for engaging a network of noncovalent attractive interactions to facilitate the cyclopropanation process. The Co(II)-based metalloradical system is capable of activating different alkynyldiazomethanes under mild conditions for highly asymmetric cyclopropanation of diverse alkenes with varied electronic and steric properties, affording chiral alkynyl cyclopropanes in high yields with high both diastereoselectivity and enantioselectivity. The combined computational and experimental studies have shed light on the underlying stepwise radical mechanism of the Co(II)-based cyclopropanation system involving a unique α-metalloradical intermediate that is associated with two resonance forms of α-Co(III)-propargyl radical and γ-

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Co(III)-allenyl radical. In addition to rationalizing the unique profile of reactivity and selectivity, the established mechanism offers a convincing explanation of the regioselectivity toward the formation of alkynyl cyclopropanes via α-Co(III)-propargylic radical form without any complication from potential reaction via γ-Co(III)-allenyl radical form. The resulting enantioenriched alkynyl cyclopropanes, as showcased in several stereospecific transformations, may serve as useful intermediates for stereospecific organic synthesis. Considering the ubiquity of chiral alkynyl cyclopropanes, we believe this Co(II)-catalyzed asymmetric radical cyclopropanation process will find useful applications in organic synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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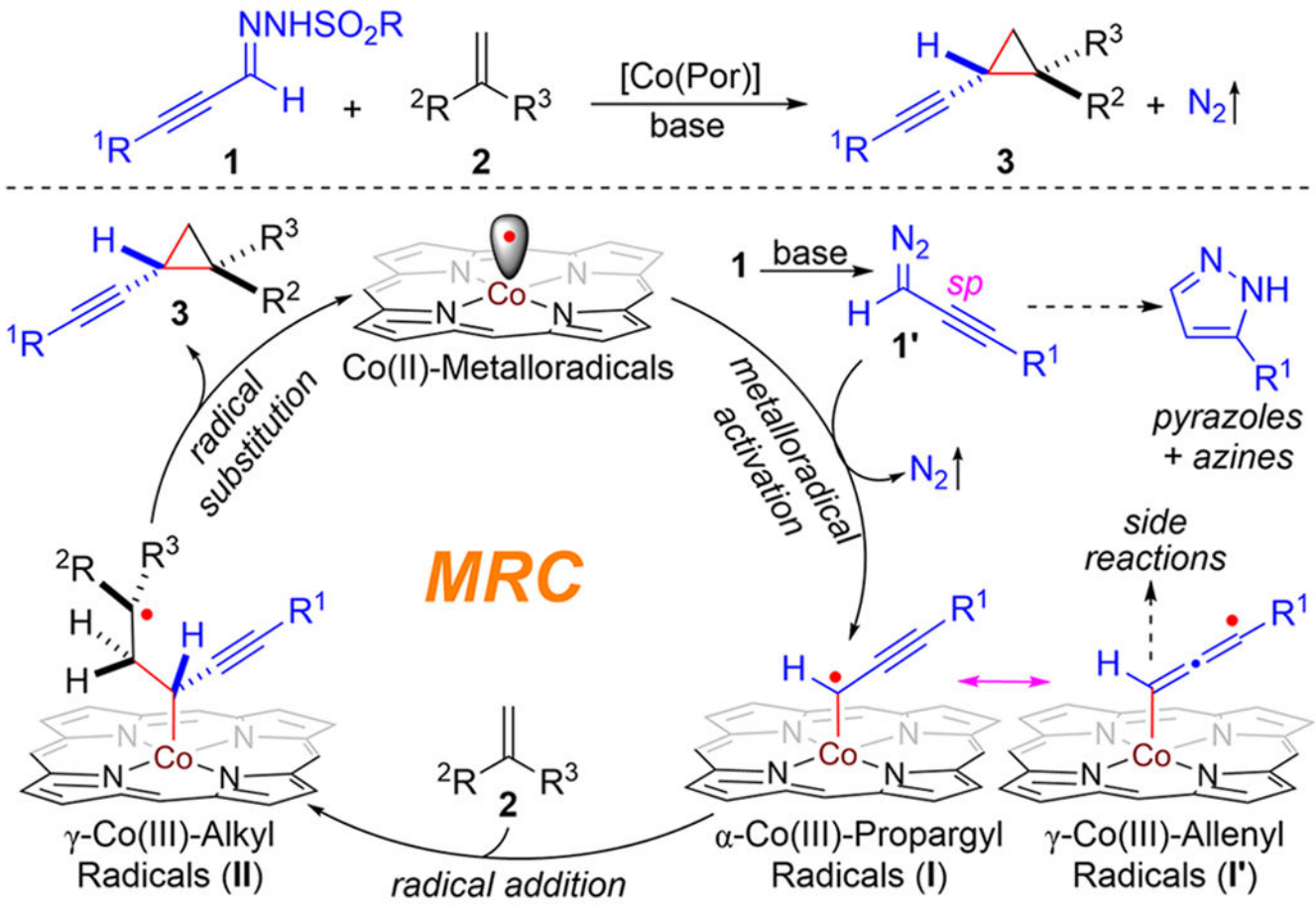

Scheme 1.

Proposed Pathway for Radical Cyclopropanation of Alkenes with α-Alkynyldiazomethanes via Co(II)-MRC

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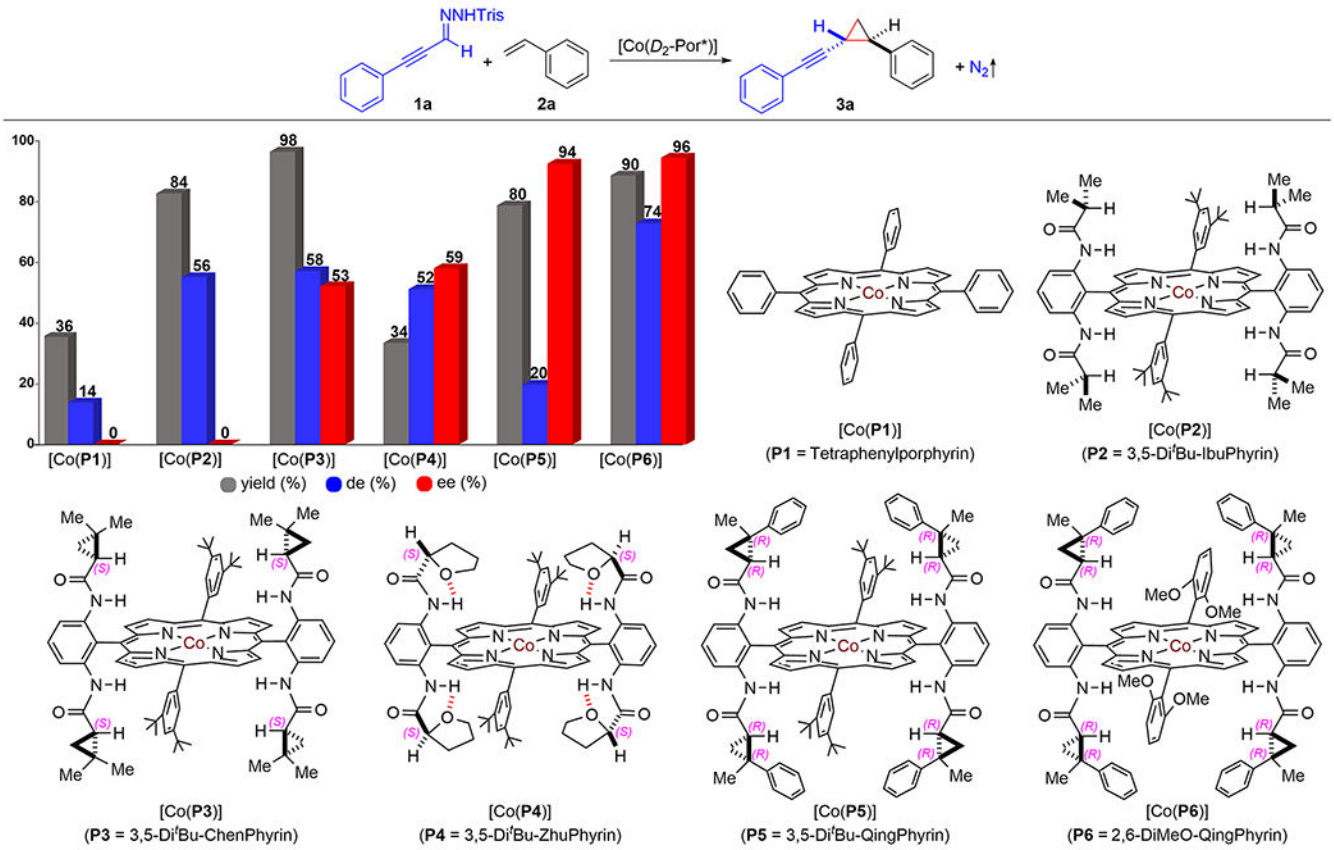

Scheme 2. Ligand Effect on Co(II)-Based Catalytic System for Olefin Cyclopropanation with Alkynyldiazomethane[a]

[a] Carried out with **1a** (0.10 mmol) and **2a** (0.20 mmol) in the presence of KH (0.40 mmol) by [Co(Por)] (2 mol %) in ethyl acetate (0.6 mL) at 22 °C for 24 h; Tris = 2,4,6-triisopropylbenzenesulfonyl; isolated yields; diastereomeric excess (de) determined by ^{1}H NMR; enantiomeric excess (ee) of *trans*-isomer determined by chiral HPLC.

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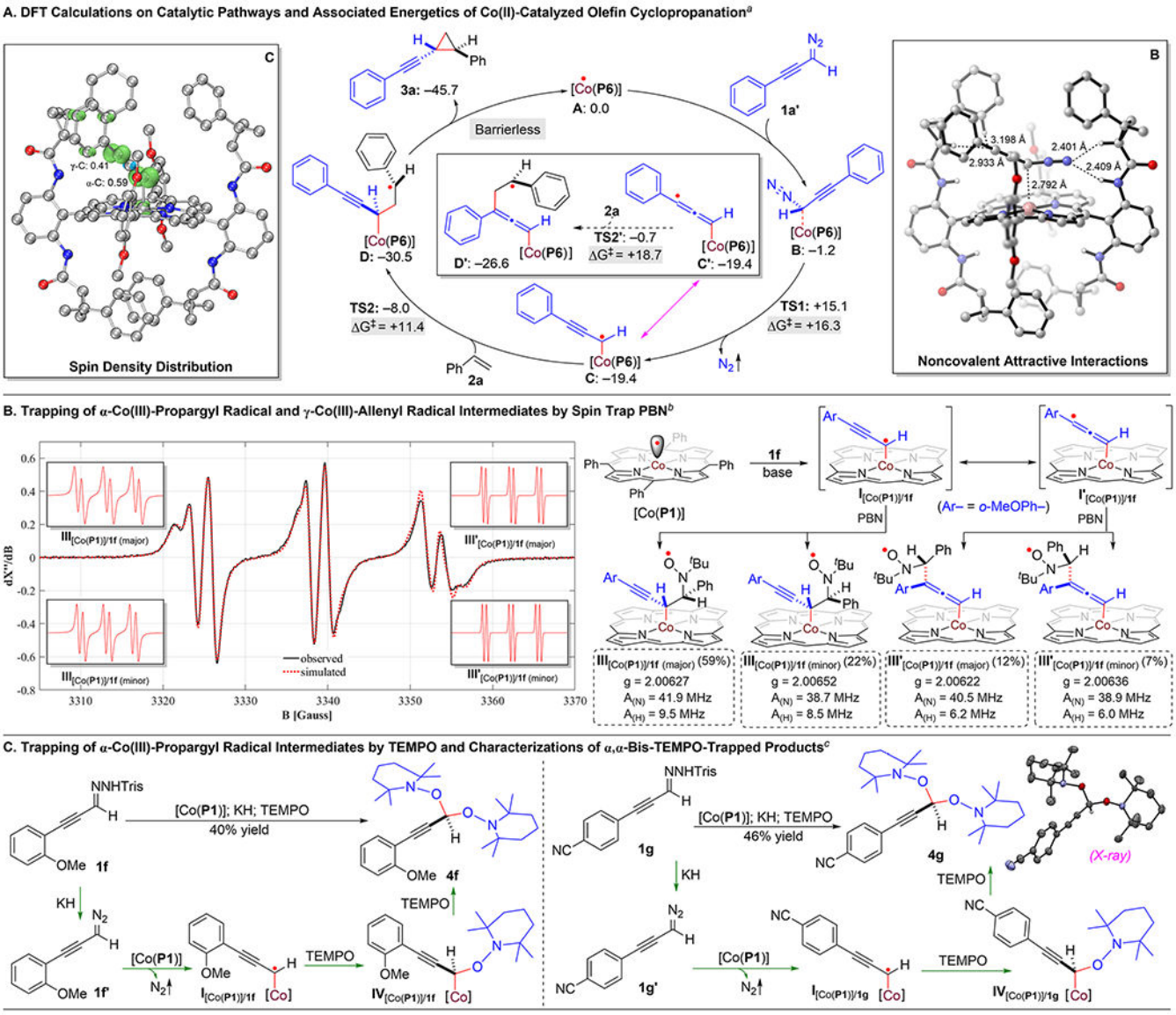

Scheme 3. Mechanistic Studies on Co(II)-Catalyzed Olefin Cyclopropanation with *α*-Alkynyldiazomethanes

[a]Applied bp86/LANL2DZ for geometry optimization and B3LYP/def2-tzvp for calculations of single-point energies (kcal/mol) along with Grimme's dispersion correction and SMD (ethyl acetate) solvation model. [b]Carried out with **1f** (0.10 mmol), [Co(**P1**)] (2 mol %) and PBN (0.12 mmol) in the presence of Et_3N (0.20 mmol) at 60 °C in benzene (1.0 mL) for 10 min; Ar = 2-methoxyphenyl. The simulation of the EPR spectrum was carried out by iteration of the isotropic *g*-values and line widths using the EPR simulation program SpinFit Xenon. [c]Carried out with **1** (0.10 mmol) and TEMPO (0.60 mmol) in the presence of KH (0.40 mmol) by [Co(**P1**)] (2 mol %) in ethyl acetate (0.6 mL) at 22 °C for 24 h; Tris = 2,4,6-triisopropylbenzene sulfonyl; isolated yield; structure determined by X-ray crystallography.

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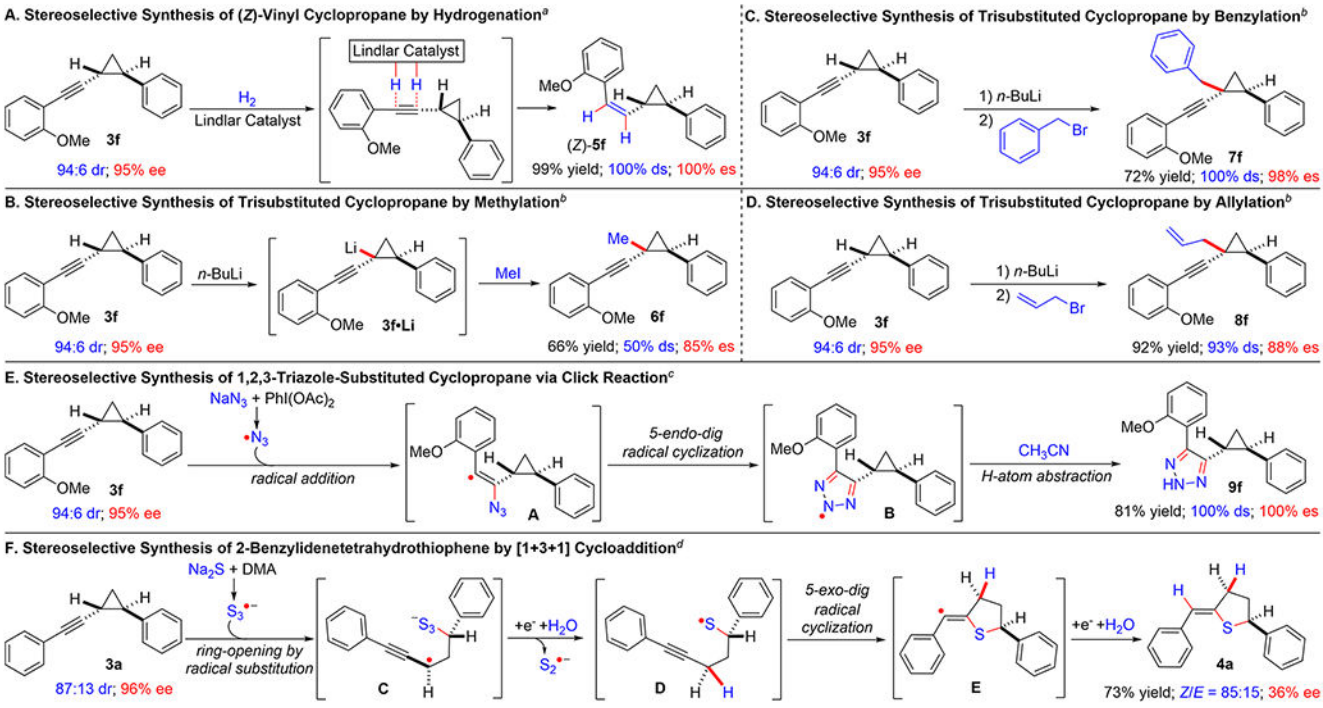

Scheme 4. Synthetic Applications of Resulting Chiral Alkynyl Cyclopropanes from Co(II)-Catalyzed Olefin Cyclopropanation

[a]Carried out with **3f** (0.10 mmol) and quinoline (2.0 equiv) by Lindlar catalyst (1.2 equiv) in mixed solvent (2.0 mL; hexane:ethyl acetate = 1:1) under H_2 atmosphere at 22 °C for 12 h. [b]Carried out with **3f** (0.10 mmol) and *n*-BuLi (1.6 equiv) in THF (2.0 mL) under N_2 atmosphere at −78 °C for 1 h, followed by addition of electrophile (1.6 equiv) and then stirred at 22 °C for 24 h. [c]Carried out with **3f** (0.10 mmol), NaN_3 (1.5 equiv), and $PhI(OAc)_2$ (1.0 equiv) in MeCN (2.0 mL) under N_2 atmosphere at 22 °C for 12 h. [d]Carried out with **3a** (0.10 mmol) and $Na_2S{\cdot}9H_2O$ (6.0 equiv) in DMA (0.5 mL) at 150 °C for 12 h.

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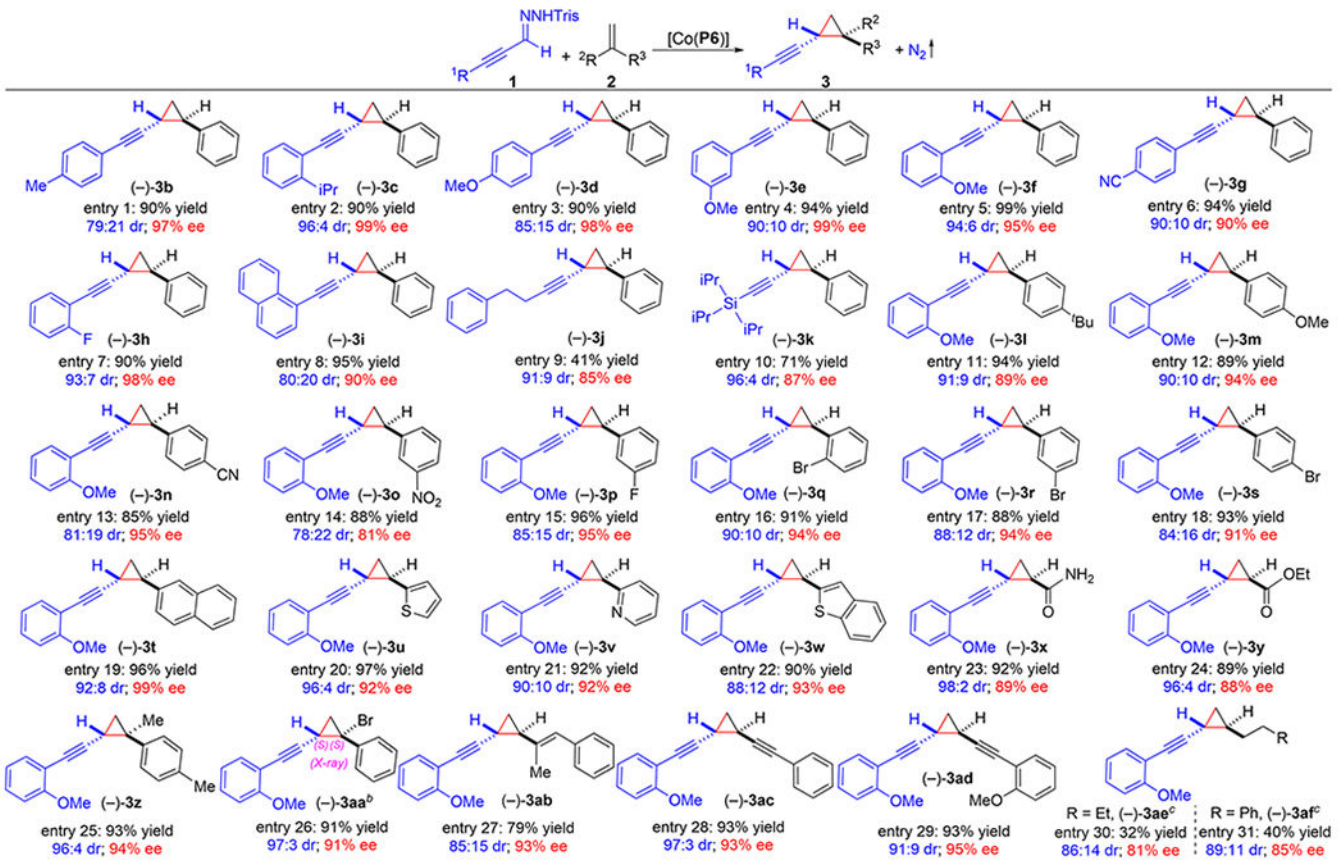
Table 1.

Scope of Catalytic Asymmetric Cyclopropanation of Alkenes with α-Alkynyldiazomethanes by [Co(P6)][a]



[a]Carried out with 1 (0.10 mmol) and 2 (0.20 mmol) in the presence of KH (0.40 mmol) by [Co(**P6**)] (2 mol %) in ethyl acetate (0.6 mL) at 22°C for 24 h; Tris = 2,4,6-triisopropylbenzenesulfonyl; isolated yields; diastereomeric ratio (dr) determined by ^{1}H NMR analysis of reaction mixture; enantiomeric excess (ee) of *trans*-isomer determined by chiral HPLC.

[b]Absolute configuration determined by X-ray crystallography.

[c]Carried out with **2** (1.00 mmol) at 80 °C.