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Controlling Enantioselectivity and Diastereoselectivity in Radical Cascade Cyclization for Construction of Bicyclic Structures

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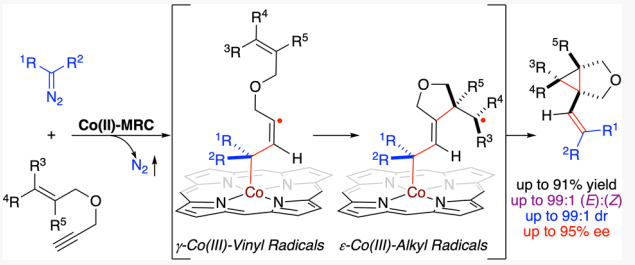
ABSTRACT: Radical cascade cyclization reactions are highly attractive synthetic tools for the construction of polycyclic molecules in organic synthesis. While it has been successfully implemented in diastereoselective synthesis of natural products and other complex compounds, radical cascade cyclization faces a major challenge of controlling enantioselectivity. As the first application of metalloradical catalysis (MRC) for controlling enantioselectivity as well as diastereoselectivity in radical cascade cyclization, we herein report the development of a Co(II)-based catalytic system for asymmetric radical bicyclization of 1,6-enynes with diazo compounds. Through the fine-tuning of D_2-symmetric chiral amidoporphyrins as the supporting ligands, the Co(II)-catalyzed radical cascade process, which proceeds in a single operation under mild conditions, enables asymmetric construction of multisubstituted cyclopropane-fused tetrahydrofurans bearing three contiguous stereogenic centers, including two all-carbon quaternary centers, in high yields with excellent stereoselectivities. Combined computational and experimental studies have shed light on the underlying stepwise radical mechanism for this new Co(II)-based cascade bicyclization that involves the relay of several Co-supported C-centered radical intermediates, including α-, β-, γ-, and ε-metalloalkyl radicals. The resulting enantioenriched cyclopropane-fused tetrahydrofurans that contain a trisubstituted vinyl group at the bridgehead, as showcased in several stereospecific transformations, may serve as useful intermediates for stereoselective organic synthesis. The successful demonstration of this new asymmetric radical process via Co(II)-MRC points out a potentially general approach for controlling enantioselectivity as well as diastereoselectivity in synthetically attractive radical cascade reactions.



INTRODUCTION

Radical cascade represents a powerful synthetic strategy to construct complex molecular structures bearing multiple stereogenic centers in a single operation.[1] Although they have often been employed for total synthesis of natural products in diastereoselective forms, control of enantioselectivity remains a formidable challenge in free radical cascade reactions.[2] Among recent advances,[3] metalloradical catalysis (MRC) offers a new catalytic approach to controlling reactivity as well as selectivity of radical reactions by generating metal-supported organic radicals as key catalytic intermediates.[1h,4−6] As stable 15e-metalloradicals, Co(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] exhibit the unusual ability to homolytically activate diazo compounds for the generation of α-Co(III)-alkyl radicals, which can serve as kinetically competent intermediates in various asymmetric radical cyclization processes.[7] Among transformations, [Co(D_2-Por*)] was shown to catalyze enantioselective radical cyclopropenation of alkynes with diazo compounds by a stepwise radical mechanism that involves product-forming 3-*exo-tet* radical cyclization of γ-Co(III)-vinyl radicals (Scheme 1A), which were formed by radical addition of initially generated α-Co(III)-alkyl radicals to the C≡C bonds.[8] To explore new reactivities of the Co-bonded vinyl radical intermediates beyond the demonstrated radical substitution for cyclopropene formation, we were attracted to the possibility of applying Co(II)-based MRC for the development of radical cascade processes by engaging the intermediates for further radical addition to C═C bonds and subsequent radical reactions, with the potential to control enantioselectivity and other stereoselectivities. Specifically, we were interested in developing asymmetric radical bicyclization of 1,6-enynes **2** with diazo compounds **1** for stereoselective construction of cyclopropane-fused tetrahydrofurans **3** (Scheme 1B). In addition to the prerequisite for generation of α-Co(III)-alkyl radicals **I** from metalloradical activation of diazo compounds **1**, it was unclear whether the intermediate **I** could undergo effective radical addition to aliphatic alkynes like **2** to form the corresponding γ-Co(III)-vinyl radicals **II** given that the previous report mainly involved the use of aryl and conjugated

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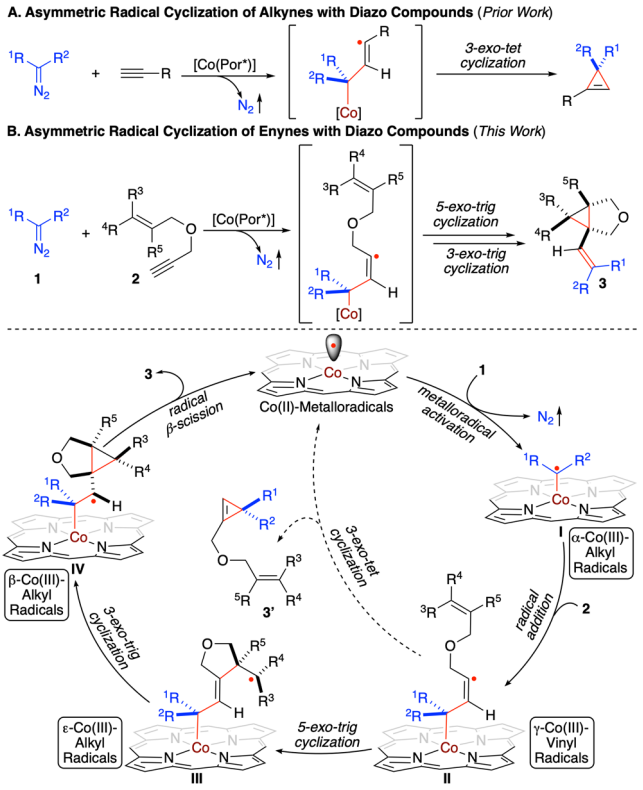
Scheme 1. Working Proposal for Radical Cascade Cyclization of 1,6-Enynes with Diazo Compounds via Co(II)-MRC



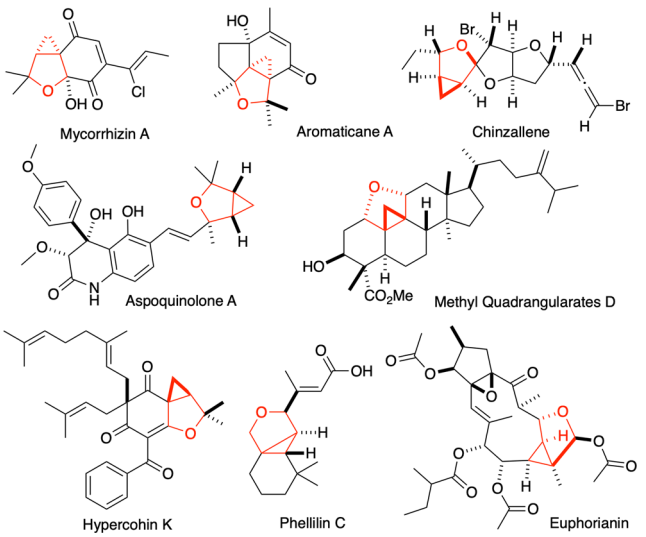


Figure 1. Selected examples of natural products and bioactive compounds containing cyclopropane-fused tetrahydrofurans.

alkynes.[8] Furthermore, to avoid the production of the undesired cyclopropenes **3′**, the vinyl radical intermediate **II** would be required to undergo competitive 5-*exo-trig* radical cyclization for formation of ε-Co(III)-alkyl radicals **III** over the previously demonstrated 3-*exo-tet* radical cyclization. Moreover, the subsequent 3-*exo-trig* radical cyclization of the alkyl radical intermediate **III** for formation of β-Co(III)-alkyl radicals **IV** might also face competitive radical processes, such as potential 5-*exo-tet* and 4-*endo-trig* cyclization reactions (Scheme S1 in the Supporting Information). Although radical β-scission is typically facile, it was an unsettled question how the α-substituents R^1 and R^2 in radical intermediate **IV** would influence the last step of the catalytic process for production of bicyclic compounds **3**. Along with the breaking and forming of the multiple bonds, the proposed radical cascade transformation would create five stereogenic centers (three sp^3-carbons plus a pair of sp^2-carbons) in the resulting 1-alkenylbicyclo[3.1.0]hexane structures **3**. Apart from the aforementioned reactivity issues, how to control stereoselectivities in this radical cascade reaction, including enantioselectivity and diastereoselectivity for the three chiral centers as well as (*E*)/(*Z*) selectivity for the C=C bond, is an equally important question. We hoped to address these and related issues by fine-tuning the D_2-Por* ligand platform to adopt proper steric, electronic, and chiral environments to govern the course of the desired catalytic process. If achieved, it would lead to the development of a new catalytic process for asymmetric radical cascade cyclization to construct cyclopropane-fused tetrahydrofurans and other related 1-alkenylbicyclo[3.1.0]hexanes, which have found wide-ranging applications (Figure 1 and Figure S1).[9]

Catalytic bicyclization of 1,6-enynes with diazo compounds represents an attractive method to construct 1-alkenylbicyclo[3.1.0]hexane structures such as cyclopropane-fused tetrahydrofurans with potential control of stereoselectivities.[10] Among advances in the realm, Dixneuf and co-workers reported the first Ru-based catalytic system for diastereoselective synthesis of 1-alkenylbicyclo[3.1.0]hexane derivatives from bicyclization of 1,6-enynes with trimethylsilyldiazomethane and ethyl diazoacetate.[10a,b,d−f] Montgomery and Ni also developed a Ni-catalyzed system for diastereoselective synthesis of 1-alkenylbicyclo[3.1.0]hexanes, including cyclopropane-fused tetrahydrofurans, from cycloaddition of 1,6-enynes with trimethylsilyldiazomethane.[10c] Liu and co-workers subsequently developed Au-catalyzed system for diastereoselective synthesis of cyclopropane-fused tetrahydrofuran derivatives from reaction of 1,6-enynes with diazoketones.[10g] Zeng and co-workers later reported diastereoselective synthesis of cyclopropane-fused pyrrolidine derivatives through Rh-catalyzed cyclization of 1,6-enynes with α-diazocarbonyl compounds.[10h] More recently, Chen and co-workers employed Au-catalyzed diastereoselective bicyclization of 1,6-enynes with α-aryl-α-diazoacetates to generate 1-alkenylbicyclo[3.1.0]-hexanes.[10i] Despite these advances in diastereoselective synthesis, asymmetric catalytic systems for stereoselective construction of 1-alkenylbicyclo[3.1.0]hexanes such as cyclopropane-fused tetrahydrofurans with control of enantioselectivity remain to be developed. As a new application of Co(II)-based MRC, we herein report the development of the first asymmetric catalytic system for radical cascade cyclization of 1,6-enynes with diazo compounds that enables stereoselective construction of multisubstituted cyclopropane-fused tetrahydrofurans bearing three contiguous stereogenic centers, including two all-carbon quaternary centers. In addition to practical attributes such as operational simplicity and mild conditions, we show that the Co(II)-catalyzed bicyclization proceeds through a fundamentally different mechanism from previous catalytic systems involving metallocarbene intermediates. Our combined experimental and computational studies unveil a stepwise radical mechanism that involves α-Co(III)-alkyl radicals as the key intermediate and its translocation among several different Co-supported C-centered radicals,

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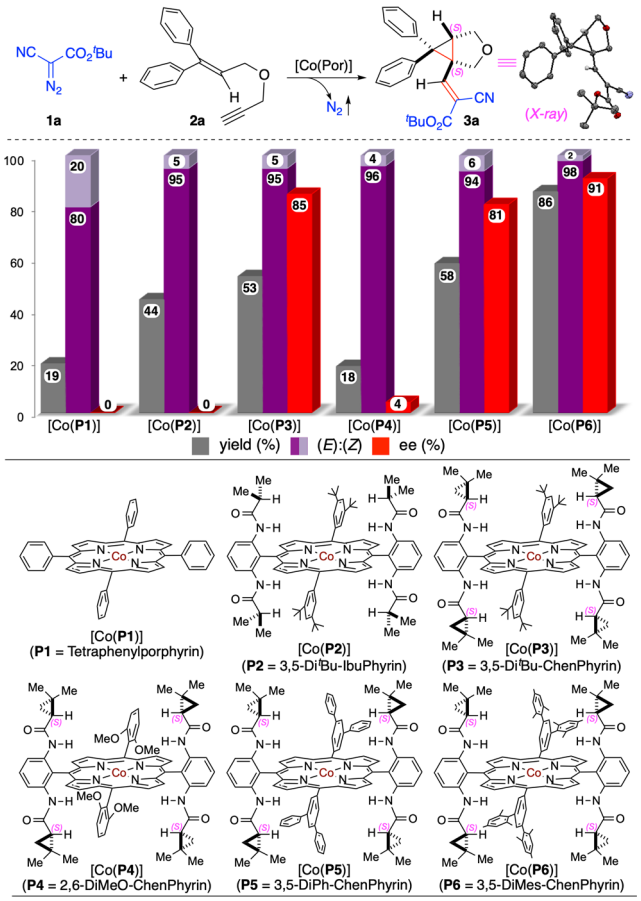
including β-, γ- and ε-Co(III)-alkyl radicals. We further show that the resulting enantioenriched cyclopropane-fused tetrahydrofurans that contain a trisubstituted vinyl group at the bridgehead are useful intermediates for stereoselective organic synthesis.

RESULTS AND DISCUSSION

Catalyst Development. At the outset of this project, 1,1-diphenyl-1,6-enyne **2a** was chosen as the model substrate for investigation of the proposed radical cascade process by Co(II)-based metalloradical catalysts with *tert*-butyl α-cyanodiazoacetate (**1a**) as the radical precursor (Scheme 2 and Table S1). It was found that the simple achiral catalyst [Co(**P1**)] (**P1** = tetraphenylporphyrin) could catalyze the formation of the desired cyclopropane-fused tetrahydrofuran **3a** but in low reactivity (19% yield) with moderate control of the olefin configuration ((*E*):(*Z*) ratio of 80:20) as the allowed *cis*-ring junction. With the use of achiral catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-IbuPhyrin),[11] which contains amide units in the supporting ligand for potential H-bonding stabilization of the corresponding α-Co(III)-alkyl radical intermediate, improvements in both yield (44%) and (*E*):(*Z*) selectivity (95:5) for product *cis*-**3a** were observed. Encouraged by these initial results, we decided to systematically investigate the ligand effect on the reactivity as well as the enantioselectivity of the Co(II)-catalyzed radical cascade cyclization. When first-generation chiral metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-ChenPhyrin) was utilized,[7a] further increase in the yield (53%) of *cis*-**3a** was attained while achieving a high level of asymmetric induction (85% ee) without affecting the high (*E*):(*Z*) selectivity (95:5). During the process of investigating the ligand effect, it was discovered that the nonchiral substituents at the *meso*-phenyl rings of ChenPhyrin ligand have a significant influence on both reactivity and enantioselectivity of the catalytic reaction. While the use of catalyst [Co(**P4**)] (**P4** = 2,6-DiMeO-ChenPhyrin) containing two methoxy groups at the proximal 2,6-positions of the *meso*-phenyl units resulted in dramatic diminishment in both yield (18%) and enantioselectivity (4% ee), [Co(**P5**)] (**P5** = 3,5-DiPh-ChenPhyrin) bearing two phenyl groups at the 3,5-positions further improved the yield (58%) without significantly affecting the enantioselectivity (81% ee). This positive outcome prompted us to fine-tune the substituents at 3,5-positions of the ChenPhyrin ligand. Excitingly, when [Co(**P6**)] (**P6** = 3,5-DiMes-ChenPhyrin) bearing two mesityl groups at 3,5-positions was used as the catalyst, it afforded cyclopropane-fused tetrahydrofuran **3a** in high yield (86%) with excellent enantioselectivity (91% ee) as well as with near-complete configurational control of the newly formed trisubstituted alkene ((*E*):(*Z*) ratio of 98:2) at the bridgehead of the allowed *cis*-ring junction of the bicyclic structure. Considering that [Co(**P6**)] differs from [Co(**P5**)] only by the distal methyl groups at the 2′,4′,6′-positions of the 3,5-positions of the phenyl group in the *meso*-phenyl units of the porphyrin core, these remarkable results signify the immense power of judicious tuning of ligand environment in controlling reactivity and stereoselectivity of the Co(II)-based metalloradical system. It is worth mentioning that ChenPhyrin ligands **P3**−**P6** could be modularly synthesized in three steps from readily available starting materials by following the previously established procedures.[7a] The absolute configurations of stereogenic centers in **3a** were confirmed by X-ray crystallography as (*S*,*S*) and (*E*), respectively (Scheme 2). Among interesting structural features, the trisubstituted (*E*)-olefin unit is almost coplanar with the tetrahydrofuran ring, which is nearly perpendicular to the pentasubstituted cyclopropane plane.

Scheme 2. Ligand Effect on Co(II)-Catalyzed Radical Cascade Cyclization of 1,6-Enyne with α-Cyanodiazoacetate[a]



[a]Carried out with **1a** (0.12 mmol) and **2a** (0.10 mmol) by [Co(Por)] (5 mol %) in CH_3CN (0.25 mL) at 40 °C for 16 h; isolated yields; only *cis*-ring junction product formed; (*E*):(*Z*) of olefin configuration determined by ^{1}H NMR; enantiomeric excess (ee) determined by chiral HPLC.

Substrate Scope. Under the optimized conditions, the scope of the [Co(**P6**)]-catalyzed radical bicyclization with *tert*-butyl α-cyanodiazoacetate (**1a**) was then evaluated by employing different 1,6-enynes **2** (Table 1). Like 1,1-diphenyl-1,6-enyne **2a** (entry 1), 1,1-diaryl-1,6-enynes containing various aryl groups with substituents at different positions, such as *p*-OMe (**2b**), *p*-F (**2c**), and *m*-F (**2d**), could be bicyclized with **1a** by [Co(**P6**)], affording the corresponding cyclopropane-fused tetrahydrofurans (+)-**3b**, (+)-**3c**, and (+)-**3d** as the allowed *cis*-ring junction in good to high yields with excellent (*E*):(*Z*) selectivities and enantioselectivities (entries 1−4). It is worth mentioning that the catalytic radical cascade process could be readily scaled up as demonstrated with the bicyclization reaction of **2a** with **1a** on a 2.0 mmol scale, delivering optically active compound (+)-*cis*-**3a** in 86% yield with 98:2 (*E*):(*Z*) and 91% ee (entry 1). Both (*E*)- and (*Z*)-1,1-diaryl-1,6-enynes containing the *p*-OMe substituted aryl group ((*E*)-**2e** and (*Z*)-**2f**) underwent radical cascade

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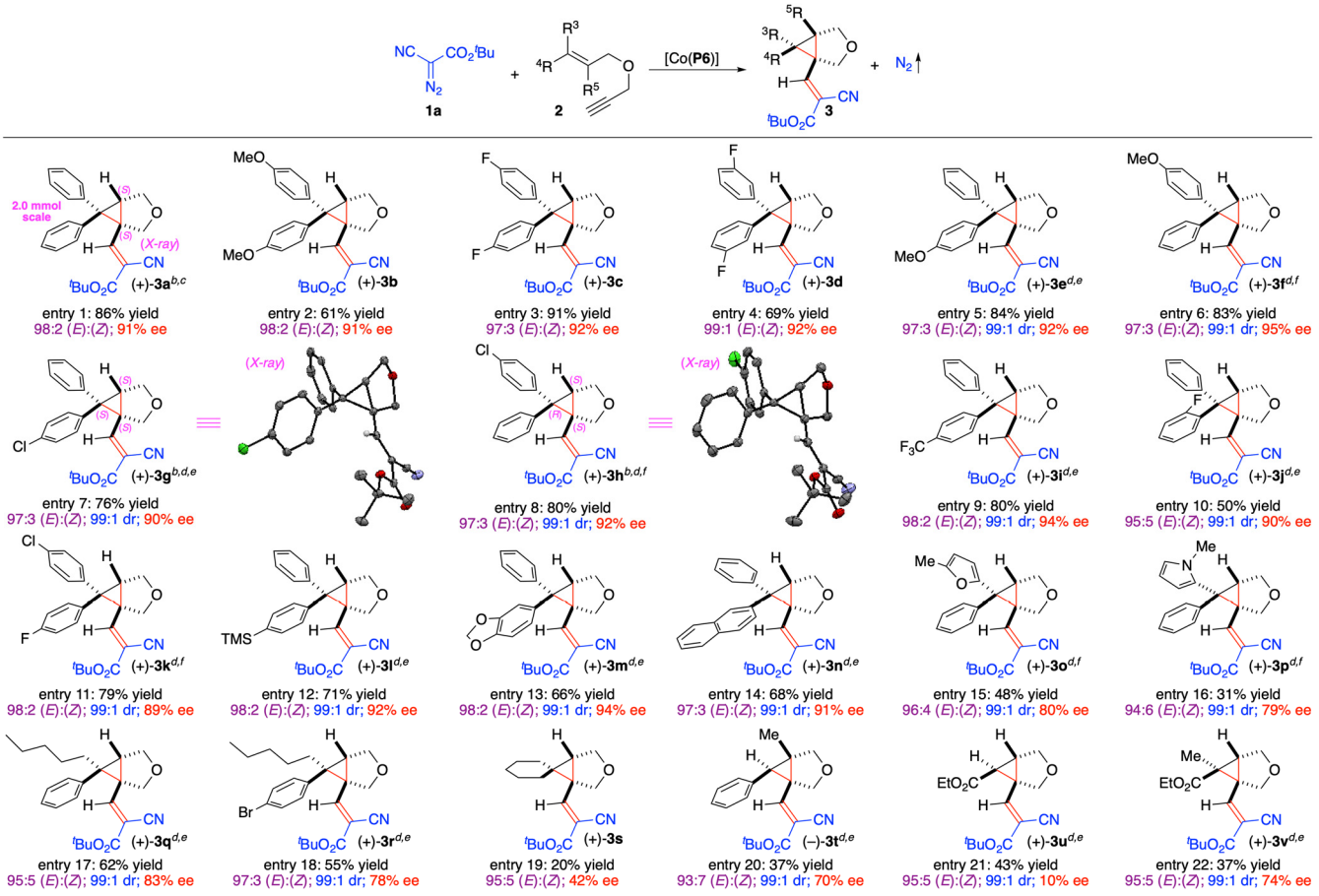
Table 1. Asymmetric Radical Bicyclization of 1,6-Enynes with *tert*-Butyl α-Cyanodiazoacetate Catalyzed by [Co(P6)][a]



[a]Carried out with **1a** (0.12 mmol) and **2** (0.10 mmol) by [Co(**P6**)] (5 mol %) in CH_3CN (0.25 mL) at 40 °C for 16 h; isolated yields; only *cis*-ring junction product formed; (*E*):(*Z*) of olefin configuration determined by ^{1}H NMR; enantiomeric excess (ee) determined by chiral HPLC. [b]Absolute configurations determined by X-ray crystallography. [c]Performed on a 2.0 mmol scale. [d]Diastereomeric ratio (dr) between *endo*- and *exo*-isomers determined by ^{1}H NMR. [e]From (*E*)-enyne. [f]From (*Z*)-enyne.

process stereospecifically to afford the corresponding (+)-**3e** and (+)-**3f** as *exo*- and *endo*-isomers, respectively (entries 5 and 6). The same stereospecific transformations were observed for (*E*)- and (*Z*)-1,1-diaryl-1,6-enynes containing *p*-Cl-substituted aryl group ((*E*)-**2g** and (*Z*)-**2h**), offering the relevant (+)-**3g** and (+)-**3h** as *exo*- and *endo*-isomers, respectively (entries 7 and 8). The absolute configurations of (+)-**3g** and (+)-**3h** were established as (*S*,*S*,*S*) and (*R*,*S*,*S*), respectively, by X-ray crystallography, confirming the stereospecificity of the transformations. Likewise, 1,1-diaryl-1,6-enynes substituted with different aryl groups ((*E*)-**2i**, (*E*)-**2j**, (*Z*)-**2k**, (*E*)-**2l**, and (*E*)-**2m**) could be stereospecifically bicyclized to generate the desired products ((+)-**3i**, (+)-**3j**, (+)-**3k**, (+)-**3l**, and (+)-**3m**) in moderate to high yields with high levels of diastereoselectivities and enantioselectivities as well as (*E*):(*Z*)-selectivities (entries 9−13). Furthermore, enyne substrates containing extended aromatic and heteroaromatic groups, including naphthalene ((*E*)-**2n**), furan ((*Z*)-**2o**), and pyrrole ((*Z*)-**2p**), were also compatible with the radical cascade cyclization, bringing about stereospecific production of the corresponding (+)-**3n**, (+)-**3o**, and (+)-**3p** (entries 14−16). Besides 1,1-diaryl-1,6-enynes, 1-aryl-1-alkyl-1,6-enynes such as (*E*)-**2q** and (*E*)-**2r** were also suitable substrates for the catalytic system, leading to stereospecific formation of cyclopropane-fused tetrahydrofurans (+)-**3q** and (+)-**3r** in good yields with excellent diastereoselectivities and good enantioselectivities (entries 17 and 18). Tricyclic structure (+)-**3s** that contains both spiro and fused rings could be constructed by the catalytic system from 1,1-dialkyl-1,6-enyne **2s** containing exocyclic alkene unit (entry 19). Notably, this cascade process was also applicable to 1,2-disubstituted 1,6-enynes such as 1-phenyl-2-methyl-1,6-enyne (*E*)-**2t**, resulting in stereospecific construction of cyclopropane-fused tetrahydrofuran (−)-**3t** bearing two all-carbon quaternary centers at both bridgeheads in moderate yield with good diastereoselectivity and enantioselectivity (entry 20). Additionally, 1,6-enynes bearing α,β-unsaturated esters as the alkene unit such as (*E*)-**2u** and (*E*)-**2v** could also be applied in the radical cascade process, affording the corresponding cyclopropane-fused tetrahydrofurans (+)-**3u** and (+)-**3v** in moderate yields with low to good enantioselectivities and high diastereoselectivities (entries 21 and 22).

Mechanistic Studies. Combined experimental and computational studies were performed to comprehend the underlying mechanism of the Co(II)-based catalytic system for cascade cyclization. To experimentally detect the first α-Co(III)-alkyl radical intermediate, the reaction solution of [Co(**P2**)] with α-cyanodiazoacetate **1a** in the absence of enyne substrate was monitored by electron paramagnetic resonance (EPR) spectroscopy at room temperature (Scheme 3A). The

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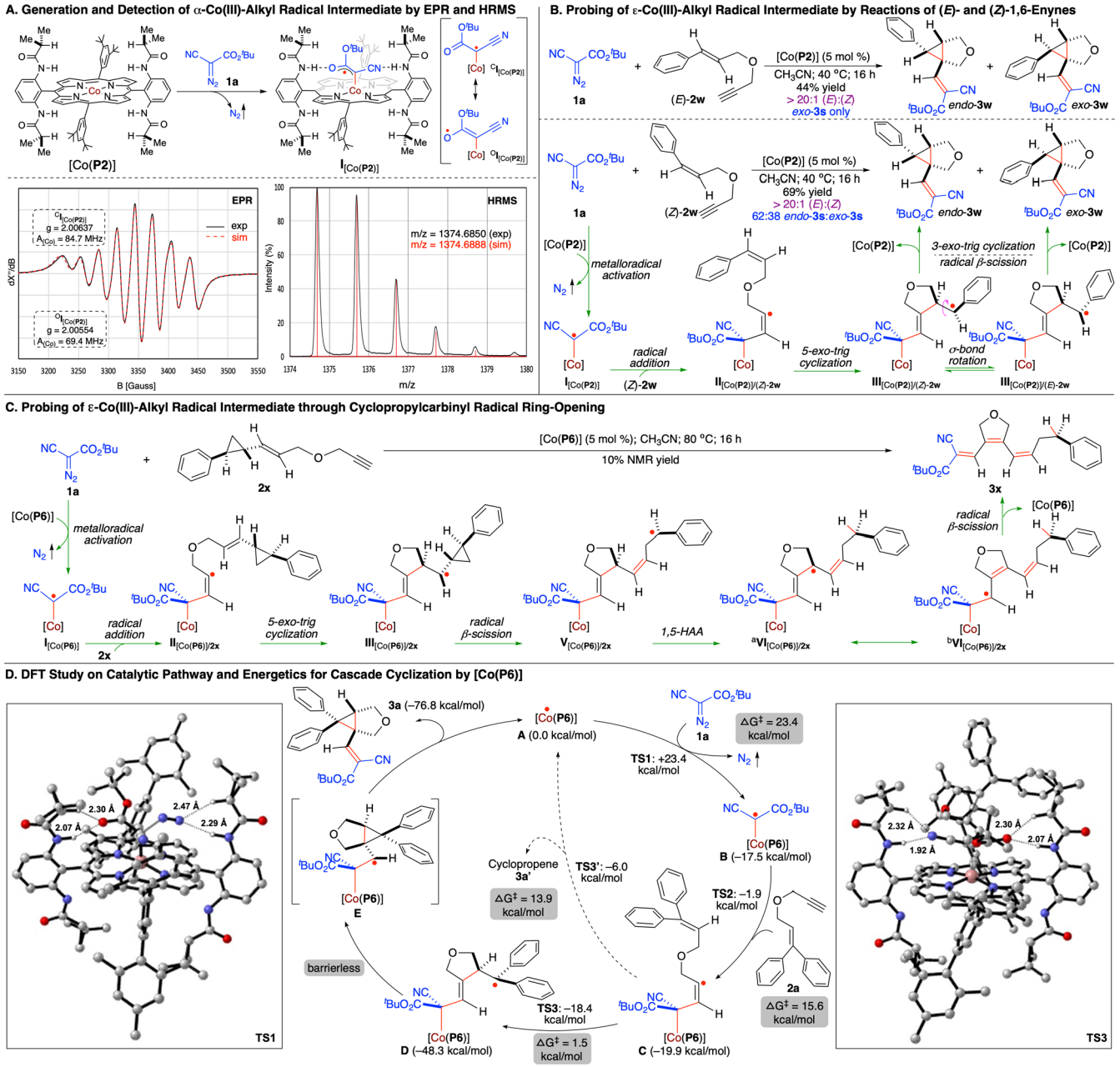
Scheme 3. Mechanistic Studies on Co(II)-Catalyzed System for Bicyclization of 1,6-Enynes with Diazo Compounds



isotropic EPR spectrum exhibits a strong signal at a *g*-value of ~2.00 as a well-resolved octet, which is diagnostic of the corresponding α-Co(III)-alkyl radical $\mathbf{I}_{[Co(P2)]}$ generated from metalloradical activation of **1a** by [Co(**P2**)]. The observed spectrum (in black) could be near perfectly simulated (in red) by involving two resonance forms of radical $\mathbf{I}_{[Co(P2)]}$ on the basis of hyperfine couplings by ^{59}Co (I = 7/2): 96% of C-centered radical at α-position $^{C}\mathbf{I}_{[Co(P2)]}$ (g = 2.00637; $A_{(Co)}$ = 84.7 MHz) and 4% of O-centered radical at γ-position $^{O}\mathbf{I}_{[Co(P2)]}$ (g = 2.00554; $A_{(Co)}$ = 69.4 MHz). Moreover, the α-Co(III)-alkyl radical $\mathbf{I}_{[Co(P2)]}$ from the reaction solution could be detected by high-resolution mass spectrometry (HRMS) with electrospray ionization (ESI). The observed mass of 1374.6850 evidently resulted from α-Co(III)-alkyl radical $\mathbf{I}_{[Co(P2)]}$ by the loss of one electron. Both the exact mass and the pattern of isotope distribution determined by ESI-HRMS match nicely with those calculated from the formula $[C_{83}H_{97}CoN_9O_6]^+$ (m/z = 1374.6888). The experimental detection of the α-Co(III)-alkyl radical $\mathbf{I}_{[Co(P2)]}$ by EPR and HRMS has provided strong evidence to support the first step of metalloradical activation in the proposed mechanism (Scheme 1).

To experimentally probe the existence of the γ-Co(III)-vinyl radical intermediate **II** and ε-Co(III)-benzyl radical intermediate **III**, both (*Z*)- and (*E*)-isomers of 1-phenyl-1,6-enyne **2w** were synthesized and subjected to the radical cascade cyclization by [Co(**P2**)] (Scheme 3B). While the reaction of (*E*)-**2w** afforded *exo*-**3w** as the only diastereomer, the radical cascade cyclization of (*Z*)-**2w** generated a diastereomeric mixture of *endo*-**3w** and *exo*-**3w** in a ratio of 62 to 38. The observation of both *endo*-**3w** and *exo*-**3w** from the reaction of (*Z*)-**2w** implies the existence of ε-Co(III)-benzyl radical $\mathbf{III}_{[Co(P2)]/(Z)\text{-}2w}$, which was generated from the 5-*exo*-*trig* cyclization of γ-Co(III)-alkyl radical intermediate

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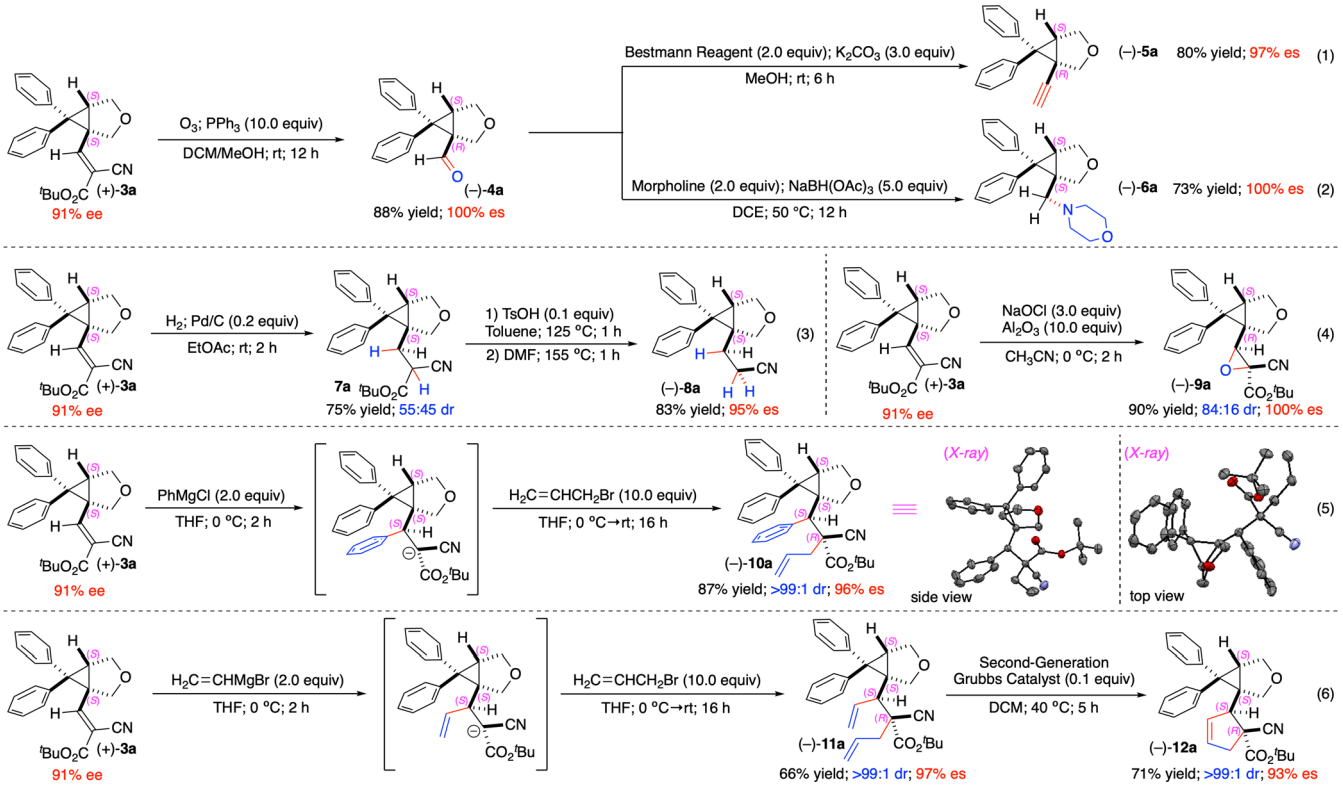
Scheme 4. Synthetic Applications of Resulting Bicyclo[3.1.0]hexanes from Co(II)-Based Asymmetric Radical Bicyclization[a]



[a]Enantiospecificity (es) determined by chiral HPLC.

$\mathbf{II}_{[Co(P2)]/(Z)\text{-}2w}$ and its conformational isomer $\mathbf{III}_{[Co(P2)]/(E)\text{-}2w}$ that resulted from σ-bond rotation (Scheme 3B). Furthermore, 1,6-enyne **2x** bearing a cyclopropyl ring was synthesized to probe the existence of the ε-Co(III)-alkyl radical intermediate through cyclopropylcarbinyl radical ring-opening (Scheme 3C). When the catalytic reaction of **2x** was conducted at elevated temperature by using [Co(**P6**)] as the catalyst, the formation of conjugated triene **3x** could be observed in 10% yield. Compound **3x** likely originated from homoallylic alkyl radical $\mathbf{V}_{[Co(P6)]/2x}$ that was generated from the ring-opening of the corresponding ε-Co(III)-cyclopropylcarbinyl radical intermediate $\mathbf{III}_{[Co(P6)]/2x}$. Presumably, radical intermediate $\mathbf{V}_{[Co(P6)]/2x}$ first proceeded via intramolecular 1,5-HAA (hydrogen atom abstraction) to deliver the δ-Co(III)-allylic radical $^{a}\mathbf{VI}_{[Co(P6)]/2x}$. And then its resonance form β-Co(III)-allylic radical intermediate $^{b}\mathbf{VI}_{[Co(P6)]/2x}$ underwent radical β-scission to give the observed product **3x**. Collectively, these experimental results (Schemes 3A–C) provided convincing evidence for the proposed stepwise radical mechanism of the Co(II)-based catalytic system for cascade cyclization.

DFT calculations were also performed to examine the details of the catalytic pathway and associated energetics for the bicyclization reaction of 1,6-enyne **2a** with α-cyano-diazoacetate **1a** with the use of the actual catalyst [Co(**P6**)] (Scheme 3D; see the Supporting Information for details). The DFT calculations indicate the formation of α-Co(III)-alkyl radical intermediate **B** ($\mathbf{I}_{[Co(P6)]}$) upon activation of diazo **1a** by [Co(**P6**)], with the generation of dinitrogen as the byproduct. The metalloradical activation, which is exergonic by 17.5 kcal/mol, has a relatively high but accessible activation barrier (**TS1**: $\Delta G^{\ddagger}$ = 23.4 kcal/mol) and is found to be the rate-determining step. As illustrated with the optimized structure of **TS1**, there exist multiple H-bonding interactions between the chiral amide units in [Co(**P6**)] and the cyano/ester groups of diazo **1a**. The subsequent radical addition of intermediate **B** to enyne **2a**, which is exergonic by 2.4 kcal/mol, has a lower activation barrier (**TS2**: $\Delta G^{\ddagger}$ = 15.6 kcal/mol), leading to the formation of the γ-Co(III)-vinyl radical intermediate **C** as the indicated (*Z*)-configuration. The presence of double-hydrogen-bonding interactions between the two amide units of the catalyst and the α-cyano/ester groups was evident in both steps of metalloradical activation and radical addition (see Scheme S6), which rigidifies the conformations of the intermediates and lowers the activation barrier of the transition states. According to the DFT calculations, intermediate **C** undergoes facile 5-*exo*-*trig* radical cyclization with an exceedingly low activation barrier (**TS3**: $\Delta G^{\ddagger}$ = 1.5 kcal/mol), which is also highly exergonic by 28.4 kcal/mol, delivering the ε-Co(III)-alkyl radical intermediate **D**. The low barrier is attributed to the multiple H-bonding interactions between the cyclopropyl amide units in the catalyst and the cyano/ester functionalities as illustrated in the optimized structure of **TS3**. In contrast, the potential cyclopropenation of the γ-Co(III)-vinyl radical **C** is found to have a significantly higher activation barrier (**TS3′**: $\Delta G^{\ddagger}$ = 13.9 kcal/mol). The large difference in activation barriers between the two competitive pathways of intermediate **C** explains the experimental absence of the cyclopropenation product. As the initial stereogenic center generated from radical addition of intermediate **B** to enyne **2a** is nonconsequential, the subsequent 5-*exo*-*trig* radical cyclization of intermediate **C** is considered as the enantio-determining step. To shed light on the asymmetric induction, the energy barrier for the transition state that leads to the formation of the minor enantiomer was

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also calculated and shown to be much higher than that for the major enantiomer (see Scheme S5 for details), which is consistent with the observed high enantioselectivity. The DFT calculations indicate that intermediate **D**, once generated, proceeds with a near barrierless 3-*exo-trig* cyclization, presumably through the potential β-Co(III)-alkyl radical intermediate **E**, to deliver the desired cyclopropane-fused tetrahydrofuran **3a** while regenerating catalyst [Co(**P6**)]. Despite considerable efforts, intermediate **E** could not be located by DFT computation, indicating that the last step of radical β-scission is exceedingly facile. The calculated catalytic pathway and associated energetics seem in good agreement with the experimental observations for the Co(II)-based catalytic system for cascade cyclization.

Synthetic Applications. Given that the bicyclo[3.1.0]-hexane structure represents a key motif in natural products and bioactive molecules, it would be synthetically useful if the dangling trisubstituted alkene unit at the bridgehead of the resulting enantioenriched cyclopropane-fused tetrahydrofurans **3** from the Co(II)-catalyzed radical cascade cyclization could be stereoselectively transformed to other functionalities. As an initial exploration of the synthetic applications, enantioenriched cyclopropane-fused tetrahydrofuran (+)-**3a** was chosen as the model substrate for various transformations (Scheme 4). First, the alkene unit in (+)-**3a** could be converted to the formyl functionality by ozonolysis, resulting in the formation of bicyclic aldehyde (−)-**4a** in high yield with complete retention of the stereochemistry. Considering the versatility of the formyl functionality, (−)-**4a** may serve as a valuable intermediate for further transformations. For instance, treatment of (−)-**4a** with Bestmann reagent under basic conditions led to high-yielding production of bicyclic compound (−)-**5a** bearing a terminal alkyne, which is a popular motif in click chemistry for bioconjugation applications (Scheme 4, eq 1).[12] As another example, the aldehyde functionality in (−)-**4a** could undergo reductive amination with different amines by using sodium triacetoxyborohydride,[13] as shown by its productive reaction with secondary amine morpholine to generate bicyclic compound (−)-**6a** in good yield (Scheme 4, eq 2).[12] Furthermore, the trisubstituted alkene in (+)-**3a** could be productively reduced with dihydrogen on Pd/C to give α-cyanoacetate-containing compound **7a**, which could undergo decarboxylation to afford bicyclic compound (−)-**8a** bearing propanenitrile in good yield with almost full preservation of the original optical purity (Scheme 4, eq 3). In addition to the reduction, the electron-deficient olefin in (+)-**3a** could even undergo epoxidation with sodium hypochlorite in the presence of neutral alumina, furnishing tricyclic compound (−)-**9a** with the three-membered cyclic ether linked directly at the bridgehead in excellent yield with good diastereoselectivity and complete enantiospecificity (Scheme 4, eq 4).[14] Moreover, the highly electron-deficient trisubstituted conjugated alkene in (+)-**3a** could serve as an effective Michael acceptor for nucleophilic addition and subsequent alkylation, a sequential double C−C bond-forming process that would allow for the generation of two additional vicinal stereocenters. For example, the reaction of (+)-**3a** with Grignard reagent phenylmagnesium bromide, followed by addition of allyl bromide, resulted in arylation and allylation of the C═C bond, affording compound (−)-**10a** in high yield with excellent diastereoselectivity and high retention of the original enantiopurity (Scheme 4, eq 5). The configurations of the four contiguous stereogenic centers in (−)-**10a** were established by X-ray crystallography as (*S*,*S*,*S*,*R*), revealing remarkable *syn*-addition of the aryl and allyl groups to the C═C bond. This result demonstrates the effectiveness of the cyclopropane-fused tetrahydrofuran assembly as a chiral auxiliary for controlling the stereochemistry of the alkene vicinal difunctionalization process. To further showcase the synthetic application, (+)-**3a** was shown to proceed a sequential vinylation and allylation process by reacting first with vinylmagnesium bromide as the nucleophile and then with allyl bromide as the electrophile, giving rise to compound (−)-**11a** bearing four contiguous stereogenic centers in good yield with excellent diastereoselectivity and full preservation of the original enantiopurity (Scheme 4, eq 6). Subsequent ring-closing metathesis of the two terminal olefin units in (−)-**11a** with second-generation Grubbs catalyst led to effective construction of tricyclic compound (−)-**12a** with the cyclopentene linked directly at the bridgehead in good yield with high retention of enantiopurity.

CONCLUSIONS

In summary, we have demonstrated the application of metalloradical catalysis (MRC) for controlling enantioselectivity as well as diastereoselectivity in radical cascade cyclization. Applying Co(II)-based metalloradical catalysis, the first asymmetric catalytic system has been successfully developed for radical bicyclization of 1,6-enynes with diazo compounds. With the D_2-symmetric chiral amidoporphyrin 3,5-DiMes-ChenPhyrin as the optimal supporting ligand, the Co(II)-catalyzed radical cascade process enables activation of *tert*-butyl α-cyanodiazoacetate under mild conditions to react with different 1,6-enynes for asymmetric construction of multisubstituted cyclopropane-fused tetrahydrofurans bearing three contiguous stereogenic centers, including two all-carbon quaternary centers, in high yields with excellent enantioselectivities and diastereoselectivities. Combined computational and experimental studies have shed light on the underlying stepwise radical mechanism involving several Co-supported C-centered radical intermediates for the Co(II)-based cascade bicyclization. The resulting enantioenriched cyclopropane-fused tetrahydrofurans that contain a trisubstituted vinyl group at the bridgehead, as showcased in several stereospecific transformations, may serve as useful intermediates for stereoselective organic synthesis. More broadly, we hope that the successful demonstration of this Co(II)-catalyzed asymmetric radical cascade cyclization will inspire further applications of metalloradical catalysis (MRC) as a potentially general approach to controlling enantioselectivity as well as diastereoselectivity in synthetically attractive radical cascade reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04719.

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

Accession Codes

CCDC 2083358−2083361 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

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Notes

The authors declare no competing financial interest.

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