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Asymmetric Radical Process for General Synthesis of Chiral Heteroaryl Cyclopropanes

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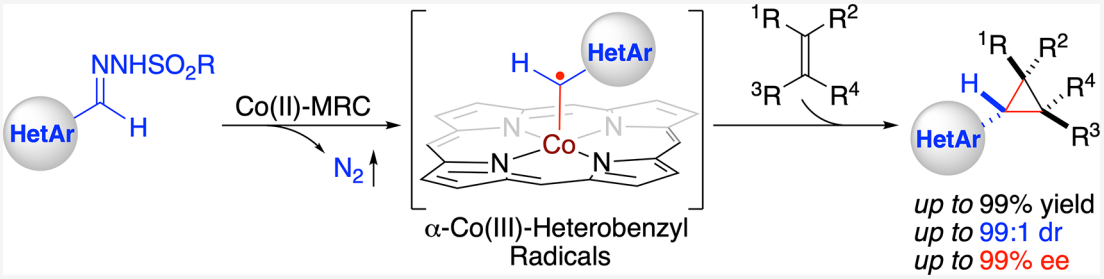

ABSTRACT: A highly efficient catalytic method has been developed for asymmetric radical cyclopropanation of alkenes with in situ-generated α-heteroaryldiazomethanes via Co(II)-based metalloradical catalysis (MRC). Through fine-tuning the cavity-like environments of newly-synthesized D_2-symmetric chiral amidoporphyrins as the supporting ligand, the optimized Co(II)-based metalloradical system is broadly applicable to α-pyridyl and other α-heteroaryldiazomethanes for asymmetric cyclopropanation of wide-ranging alkenes, including several types of challenging substrates. This new catalytic methodology provides a general access to valuable chiral heteroaryl cyclopropanes in high yields with excellent both diastereoselectivities and enantioselectivities. Combined computational and experimental studies further support the underlying stepwise radical mechanism of the Co(II)-based olefin cyclopropanation involving α- and γ-metalloalkyl radicals as the key intermediates.

INTRODUCTION

Radical chemistry has been increasingly explored for the development of new synthetic tools in modern organic synthesis.[1] Despite tremendous endeavors, long-standing challenges associated with control of reactivity and enantioselectivity remain largely unresolved for many radical reactions.[2] Among recent advances,[3] metalloradical catalysis (MRC), which involves the generation and utilization of metal-stabilized organic radicals as catalytic intermediates to harness the potential of radical chemistry, has emerged as a conceptually new approach to guide the discovery of catalytic solutions toward controlling the reactivity and stereoselectivity of radical processes.[4−6] As stable 15e-metalloradicals, cobalt(II) complexes of porphyrins ([Co(Por)]) exhibit the unique capability of homolytically activating diazo compounds to generate α-Co(III)-alkyl radicals as key intermediates for various radical transformations.[7] Specifically, with D_2-symmetric chiral amidoporphyrins (D_2-Por*) as the supporting ligands, these Co-stabilized carbon-centered radicals can engage in asymmetric radical cyclopropanation of alkenes for the preparation of optically active three-membered carbocycles.[8] While donor-substituted diazo compounds such as in situ-generated α-aryldiazomethanes have recently been demonstrated as suitable radical precursors for Co(II)-based asymmetric radical cyclopropanation,[8k,n] the analogous α-heteroaryldiazomethanes have remained underexploited for stereoselective synthesis of valuable chiral heteroaryl cyclopropanes. With this in mind, we sought to explore the feasibility of developing a catalytic process that would employ α-heteroaryldiazomethanes for asymmetric cyclopropanation of alkenes via Co(II)-MRC (Scheme 1). In view of the intrinsic properties of heteroaryl moieties, the proposed Co(II)-based catalytic process presented several fundamental challenges. Besides the concerns with efficiency of metalloradical activation of α-heteroaryldiazomethanes **1′** generated in situ from the corresponding hydrazones **1** in the presence of base, whether the subsequent radical addition of the initially formed α-Co(III)-heterobenzyl radicals **I** to the alkene substrates **2** could be rendered enantioselective is an unanswered question, primarily owing to the potential competitive coordination of the heteroaryl moieties to the metal center. On this basis, additional uncertainty of controlling reactivity and diastereoselectivity might also arise from the following 3-*exo-tet* cyclization of the resulting γ-

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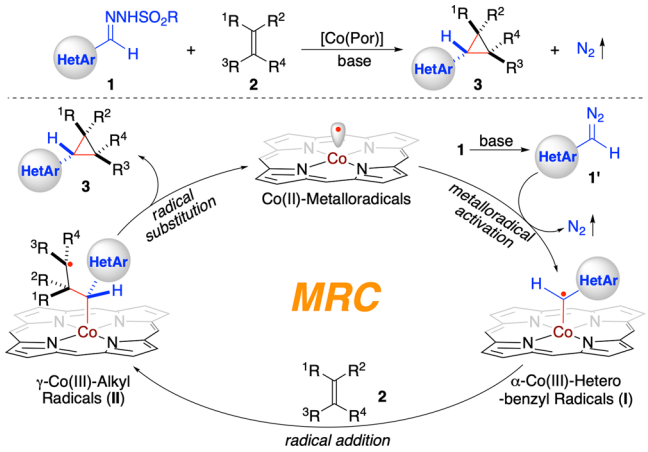
Scheme 1. Working Proposal for Synthesis of Heteroaryl Cyclopropanes from Alkenes via Co(II)-Based MRC



Co(III)-alkyl radicals **II** while forging the second C−C bond (Scheme 1). Furthermore, the presence of heteroatoms was anticipated to engage in potential H-bonding interactions with the amide units of the amidoporphyrin ligands that could pose potential complication in controlling both reactivity and selectivity in these Co(II)-based radical processes. To address these and related issues, we envisioned the prospect of designing a suitable D_2-symmetric chiral amidoporphyrin ligand with proper steric, electronic, and chiral environments that could direct the Co(II)-based catalysis for productive cyclopropanation with effective stereocontrol. If realized, it would enable the development of a new catalytic system for asymmetric olefin cyclopropanation with in situ-generated α-heteroaryldiazomethanes to furnish chiral heteroaryl cyclopropanes **3**, which are ubiquitous structural motifs in many pharmaceuticals and biologically important molecules (see Figure S1 in Supporting Information).[9]

Transition-metal catalyzed asymmetric cyclopropanation of alkenes with heteroaryldiazomethanes represents an appealing approach for the synthesis of valuable chiral heteroaryl cyclopropanes with the potential to control both diastereoselectivity and enantioselectivity.[9b,10] In contrast to the well-precedented asymmetric cyclopropanation with other types of diazo compounds,[11] only a few catalytic systems involving the use of heteroaryldiazomethanes have been reported.[12] This underdevelopment is largely attributed to their inherent instability as well as high propensity for unwanted formal dimerization.[12,13] Moreover, it is known that rhodium- and other existing metal-based catalytic systems of cyclopropanation could suffer from the notorious catalyst poisoning effect in the presence of nitrogen- and sulfur-containing heterocycles.[9b,10g] Recently, Chattopadhyay and co-workers[14f] reported a [Co(TPP)]-catalyzed (TPP = 5,10,15,20-tetraphenylporphyrin) metalloradical cyclopropanation with 2-pyridyldiazomethanes, which could be generated in situ from readily accessible *N*-tosylhydrazone precursors in the presence of base.[14] While this in situ protocol offers a novel alternative for catalytic synthesis of 2-pyridylcyclopropanes in their racemic forms, the enantioselective variant of this transformation is an attractive process that remains elusive. In addition to 2-pyridylcyclopropanes, it would be desirable to develop new catalytic systems that are generally applicable for stereoselective synthesis of diverse types of chiral heteroaryl cyclopropanes. We herein report the development of a new Co(II)-based catalytic system that is highly efficient for asymmetric cyclopropanation of alkenes with in situ-generated α-heteroaryldiazomethanes. Through the support of a new bridged D_2-symmetric chiral amidoporphyrin ligand, the Co(II)-catalyzed system allows for efficient activation of 2-pyridyldiazomethanes and other common α-heteroaryldiazomethanes for asymmetric cyclopropanation of a broad range of alkenes, affording the valuable chiral heteroaryl cyclopropanes in high yields with excellent both diastereoselectivities and enantioselectivities. Furthermore, we present detailed computational and experimental studies that shed light on the underlying stepwise radical mechanism.

RESULTS AND DISCUSSION

Catalyst Development. At the outset of this project, 2-pyridyldiazomethane (**1a'**), which was in situ generated from the corresponding tosylhydrazone **1a** in the presence of Cs_2CO_3, was investigated as the representative α-heteroaryldiazomethane for asymmetric radical cyclopropanation of styrene (**2a**) by Co(II)-based metalloradical catalysts [Co(Por)] (Scheme 2). It was found that the Co(II) complex of D_{2h}-symmetric achiral amidoporphyrin [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-IbuPhyrin)[15] could effectively catalyze the cyclopropanation reaction to afford the desired 2-pyridylcyclopropane **3a** in nearly quantitative yield (99%) with moderate diastereoselectivity (44% de). To evaluate the feasibility of asymmetric induction during the proposed catalytic cycle, Co(II) complexes of a series of D_2-symmetric chiral amidoporphyrin ligands [Co(D_2-Por*)] were employed as the catalysts. While first-generation chiral metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-ChenPhyrin)[8a] could furnish **3a** in a similarly high yield (95%) with higher diastereoselectivity (72% de), it only exhibited insignificant asymmetric induction (5% ee). Switching to second-generation metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-Tao(^{t}Bu)-Phyrin)[16] bearing chiral amide units with ester moieties resulted in the formation of **3a** in 86% yield with further improved diastereoselectivity (88% de) and a significant level of enantioselectivity (40% ee). To further enhance the asymmetric induction of this catalytic system, we then turned our attention to new-generation metalloradical catalysts [Co(HuPhyrin)], the Co(II) complexes of bridged D_2-symmetric chiral amidoporphyrins featuring more rigid cavity-like environments. When the C_6-bridged [Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-Hu(C_6)Phyrin)[16] was employed as the catalyst under the same conditions, it indeed enhanced both reactivity and stereoselectivities of the cyclopropanation reaction substantially, generating **3a** in high yield (94%) with excellent both diastereoselectivity (98% de) and enantioselectivity (92% ee). Subsequent use of analogous catalyst [Co(**P5**)] (**P5** = 2,6-DiMeO-Hu(C_6)Phyrin),[17] which bears 2,6-dimethoxyphenyl instead of 3,5-di-*tert*-butylphenyl groups as the 5,15-diaryl substituents, led to the production of **3a** in a comparable yield (91% yield) with the same stereoselectivities (98% de and 92% ee). Aiming at further improving the catalytic system, we synthesized a new C_6-bridged catalyst [Co(**P6**)] (**P6** = 2,6-DiPhO-Hu(C_6)Phyrin) by replacing the methoxy groups in **P5** with phenoxy groups. Gratifyingly, [Co(**P6**)] could catalyze the cyclopropanation reaction to afford 2-pyridylcyclopropane **3a** in almost quantitative yield (99%) with high diastereoselectivity (92% de) and outstanding enantioselectivity (99% ee).

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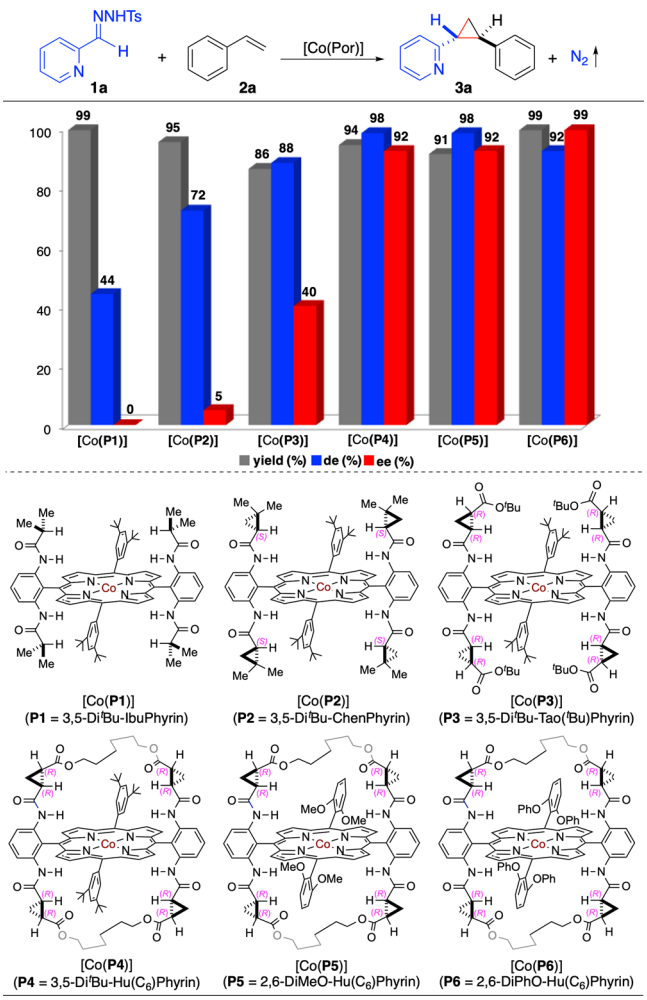
Scheme 2. Ligand Effect on Co(II)-Catalyzed Radical Cyclopropanation of Styrene with 2-Pyridyldiazomethanes[a]



[a]Carried out with **1a** (0.10 mmol), **2a** (0.15 mmol), and Cs_2CO_3 (0.20 mmol) using [Co(Por)] (2 mol %) in toluene (1.0 mL) at 80 °C for 16 h; Isolated yields; Diastereomeric excess (de) determined by ^1H NMR of crude reaction mixture; Enantiomeric excess (ee) of the major (*E*)-isomer determined by chiral HPLC; Ts = 4-toluenesulfonyl.

Substrate Scope. Under the optimized conditions, the scope and versatility of [Co(**P6**)]-catalyzed asymmetric cyclopropanation with in situ-generated 2-pyridyldiazomethane (**1a'**) were explored by employing different types of alkenes as the substrates (Table 1). Like formation of **3a** from styrene (entry 1), its derivatives bearing electron-donating and electron-withdrawing aryl substituents could also be effectively cyclopropanated by [Co(**P6**)] with **1a'**, producing the desired cyclopropanes **3b** and **3c** in similarly high yields and stereoselectivities (entries 2 and 3). The absolute configuration of the major enantiomer of **3b** was established as (*R*,*R*). Additionally, this [Co(**P6**)]-based metalloradical system was shown to tolerate various functional groups as exemplified by the stereoselective formation of **3d**−**3f** containing aryl substituents of halogen, pinacolborane, and formyl functionalities at different positions (entries 4−6). Besides monosubstituted olefins, 1,1-disubstituted olefins like α-substituted styrenes could serve as suitable substrates as well, affording the trisubstituted cyclopropanes **3g** and **3h** with excellent control of the newly generated quaternary stereogenic centers (entries 7 and 8). In addition to the extended aromatic olefins such as formation of **3i** from 2-vinylnaphthalene (entry 9), both conjugated dienes and enynes could be regio- and chemoselectively cyclopropanated to form cyclopropanes **3j**−**3l** in high yields with excellent stereoselectivities (entries 10−12). The Co(II)-based cyclopropanation was further highlighted by its unique reactivity toward various heteroaromatic olefins as shown with the highly stereoselective synthesis of 1,2-bisheteroaryl cyclopropanes **3m**−**3t** containing pyridine, thiophene, benzofuran, benzothiophene, indole, and quinoline (entries 13−20). Given that both heteroarene and cyclopropane are prevalent structural motifs in bioactive compounds, the access of bisheteroaryl cyclopropanes in high enantiopurity may find potential applications in drug research and development. Moreover, electron-deficient olefins such as acrylketones, acrylates, acrylamides, and acrylonitriles, which are known to be challenging substrates, could all be utilized for asymmetric cyclopropanation by [Co(**P6**)], furnishing the functionalized electrophilic cyclopropanes **3u**−**3z** in high yields with excellent control of stereoselectivities (entries 21−26). Similar to electron-deficient olefins, the catalytic cyclopropanation could also be applied to electron-rich olefins such as vinyl benzoate and vinyl propyl ether for highly stereoselective formation of cyclopropyl ester **3aa** and cyclopropyl ether **3ab** albeit in relatively lower yields (entries 27 and 28). Notably, the [Co(**P6**)]-based system proved to be similarly effective for the asymmetric cyclopropanation of aliphatic olefins, affording the alkyl-substituted pyridylcyclopropanes **3ac** and **3ad** in moderate yields with moderate to excellent stereoselectivities (entries 29 and 30). Gratifyingly, internal olefins such as indene and benzofuran, which are typically challenging substrates for asymmetric cyclopropanation due to steric factors, could also be cyclopropanated to form the fused cyclopropanes **3ae** and **3af** in moderate yields with high enantioselectivities despite varied diastereoselectivities (entries 31 and 32). It is worth mentioning that the Co(II)-based system was amenable to late-stage derivatization of biologically complex molecules as exemplified by the high-yielding formation of cyclopropane derivative of estrone **3ag** with excellent diastereoselectivity (entry 33).

In addition to the representative 2-pyridyldiazomethane (**1a'**), it was demonstrated that metalloradical catalyst [Co(**P6**)] could effectively activate different types of α-heteroaryldiazomethanes for asymmetric cyclopropanation of alkenes (Table 1). For instance, 3-pyridyldiazomethane (**1b'**) generated from the corresponding trishydrazone (2,4,6-triisopropylbenzenesulfonyl hydrazone) was found to be a competent radical precursor even at room temperature for the Co(II)-based asymmetric cyclopropanation. As shown with styrene (monosubstituted olefin), α-bromostyrene (1,1-disubstituted olefin), 1-phenyl-1,3-butadiene (conjugated diene), and methyl acrylate (electron-deficient olefin) as representative substrates, [Co(**P6**)] could effectively activate in situ-generated **1b'** at room temperature for highly asymmetric cyclopropanation reactions, leading to productive formation of the corresponding 3-pyridylcyclopropanes **3ah**, **3ai**, **3aj**, and **3ak** with exceptional control of stereoselectivities (entries 34−37). Likewise, other heteroaryldiazomethanes, including those generated in situ from the trishydrazones derived from 5-bromo-3-pyridyl, 4-pyridyl, 3-thienyl, 3-indolyl, and 3-quinolinyl carboxaldehydes, were all shown to be effective radical precursors for [Co(**P6**)]-catalyzed asymmetric olefin

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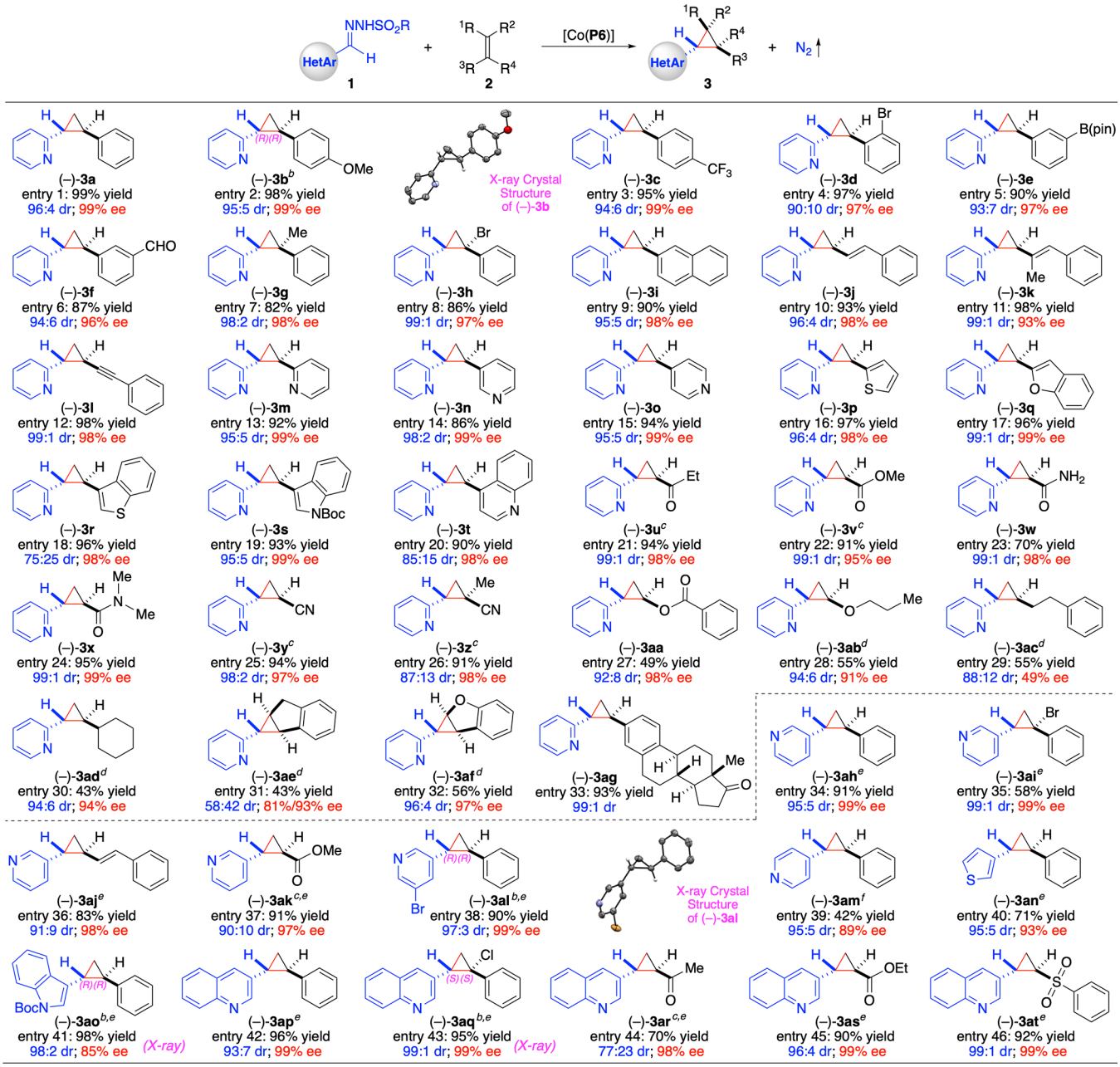
Table 1. Scope of Co(II)-Catalyzed Asymmetric Radical Cyclopropanation of Alkenes with Heteroaryldiazomethanes[a]



[a]Carried out with **1** (0.10 mmol), **2** (0.15 mmol), and Cs_2CO_3 (0.20 mmol) at 80 °C for 16 h using [Co(**P6**)] (2 mol %) in toluene (1.0 mL); R = 4-methylphenyl; Isolated yields; Diastereomeric ratio (dr) determined by ^{1}H NMR of crude reaction mixture; Enantiomeric excess (ee) of the major isomer determined by chiral HPLC. [b]Absolute configuration determined by X-ray crystallography. [c]With **2** (0.30 mmol). [d]With **2** (1.0 mmol). [e]At 22 °C; R = 2,4,6-triisopropylphenyl. [f]At 60 °C.

cyclopropanation as exemplified with the room temperature reactions of styrene as the model substrate, affording the corresponding heteroaryl cyclopropanes **3al**–**3ap** in moderate to high yields with excellent stereoselectivities (entries 38–42). The absolute configurations of the newly generated stereogenic centers in **3al** and **3ao** were both established as (*R*,*R*) by X-ray crystallography. In addition, 3-quinolinyldiazomethane (**1g'**) was also investigated for Co(II)-based cyclopropanation reactions of selected alkenes ranging from α-chlorostyrene to electron-deficient olefins. Gratifyingly, almost all of these alkene substrates could be effectively cyclopropanated, allowing for the high-yielding formation of 3-quinolinylcyclopropanes **3aq**–**3at** with excellent stereoselectivities (entries 43–46). The only exception was observed for the reaction of methyl vinyl ketone, which afforded the corresponding cyclopropane **3ar** with excellent enantioselectivity but in lower yield with diminished diastereoselectivity (entry 44). The absolute configuration of the major enantiomer of **3aq** was determined to be (*S*,*S*) by X-ray crystallography.

Considering that the [Co(**P6**)]-based catalytic system could productively utilize various α-heteroaryldiazomethanes containing heteroatom at different positions, we sought to explore the possibility of employing α-aryldiazomethanes for asymmetric cyclopropanation (Table 2), which has been largely

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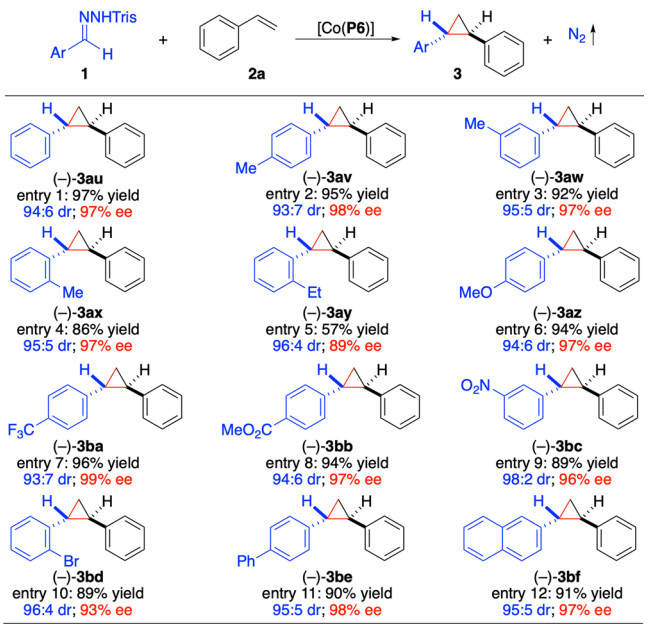
Table 2. Scope of Co(II)-Catalyzed Asymmetric Radical Cyclopropanation of Styrene with Aryldiazomethanes[a]



[a]Carried out with **1** (0.10 mmol), **2a** (0.15 mmol), and Cs_2CO_3 (0.20 mmol) using [Co(**P6**)] (2 mol %) in toluene (1.0 mL) at 22 °C for 16 h; Isolated yields; Diastereomeric ratio (dr) determined by ^{1}H NMR of crude reaction mixture; Enantiomeric excess (ee) of the major (*E*)-isomer determined by chiral HPLC; Tris = 2,4,6-triisopropylbenzene sulfonyl.

limited to those with α-aryl groups containing H-bonding acceptors at the *ortho*-position.[8k,n] To our delight, it was found that [Co(**P6**)] could effectively activate α-phenyldiazomethane (**1h'**) derived from benzaldehyde trishydrazone (**1h**) as the radical precursor for asymmetric cyclopropanation of styrene (**2a**) under the standard conditions, affording the desired 1,2-diphenylcyclopropane (**3au**) in high yield with high diastereoselectivity and excellent enantioselectivity (entry 1). Encouraged by this positive outcome, we then evaluated a wide array of α-aryldiazomethanes without H-bonding acceptors for asymmetric cyclopropanation by [Co(**P6**)]. In addition to nonsubstituted α-phenyldiazomethane, α-aryldiazomethanes bearing methyl substituent at different aryl positions, including *p*-Me (**1i'**), *m*-Me (**1j'**), and *o*-Me (**1k'**), could all be efficiently activated by [Co(**P6**)] for cyclopropanation of **2a**, furnishing the corresponding arylcyclopropanes **3av**–**3ax** in similarly high yields with the same high level of stereoselectivities (entries 2–4). Notably, the sterically encumbered *o*-ethylphenyldiazomethane (**1l'**) was found to be also suitable for the catalytic reaction, forming cyclopropane **3ay** with high stereoselectivities albeit in lower yield (entry 5). It was further shown that the [Co(**P6**)]-based system could use α-aryldiazomethanes containing substituents with varied electronic properties at different aryl positions, such as *p*-OMe (**1m'**), *p*-CF_3 (**1n'**), *p*-CO_2Me (**1o'**), and *m*-NO_2(**1p'**), for the reaction, enabling high-yielding formation of the desired cyclopropanes **3az**–**3bc** with excellent stereoselectivities (entries 6–9). Additionally, halogenated aryldiazomethanes were also suitable for the catalytic process as exemplified by the stereoselective synthesis of cyclopropane **3bd** with *o*-bromophenyldiazomethane (**1q'**) (entry 10). Furthermore, the Co(II)-based catalytic system could be applicable to α-aryldiazomethanes bearing extended aromatic systems, including *p*-biphenyldiazomethane (**1r'**) and 2-naphthyldiazomethane (**1s'**), delivering the corresponding cyclopropanes **3be** and **3bf** in high yields with excellent control of stereoselectivities. Evidently, [Co(**P6**)] represents a powerful new catalyst that is generally applicable for asymmetric olefin cyclopropanation with both α-heteroaryldiazomethanes and α-aryldiazomethanes.

Mechanistic Studies. To gain insight into the proposed stepwise radical mechanism (Scheme 1), combined computational and experimental studies were conducted (Scheme 3). 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 2-pyridyldiazomethane (**1a'**) by [Co(**P6**)] (Scheme 3A; see Supporting Information for details). The DFT calculations reveal the initial formation of intermediate **B** between the catalyst and 2-pyridyldiazomethane through multiple noncovalent attractive interactions, including H-bonding and π-stacking interactions. The noncovalent complexation, which is exergonic by 8.7 kcal/mol, positions the α-carbon atom of diazo **1a'** in close proximity to the Co(II)-metalloradical center of [Co(**P6**)] (C–Co: ~2.91 Å) for further interactions (Scheme 3A; see Scheme S7 in Supporting Information). The ensuing metalloradical activation, which is slightly exergonic by 1.2 kcal/mol, is found to be associated with a relatively high but accessible activation barrier (**TS1**: $\Delta G^{\ddagger}$ = 19.7 kcal/mol), affording α-Co(III)-pyridyl radical intermediate **C** with the release of dinitrogen as the byproduct (see Scheme S6 in Supporting Information). The subsequent radical addition of the resulting radical intermediate **C** to alkene **2a**, which is highly exergonic by 22.4 kcal/mol, proceeds through an exceedingly low activation barrier (**TS2**: $\Delta G^{\ddagger}$ = 2.3 kcal/mol), delivering γ-Co(III)-alkyl radical intermediate **D** (see Scheme S6 in Supporting Information). As illustrated in the DFT-optimized structure of **TS2** (Scheme 3A; see Scheme S7 in Supporting Information), there exists a network of noncovalent attractive interactions, such as multiple H-bonding and π-stacking interactions, between the substrates and the catalyst that synergistically lower the activation barrier of the transition state. According to the DFT calculations, the final step of 3-*exo-tet* cyclization of γ-Co(III)-alkyl radical intermediate **D**, which is exergonic by 12.6 kcal/mol (see Scheme S6 in Supporting Information), is a nearly barrierless process, leading to the formation of cyclopropane product **3a** while regenerating the metalloradical catalyst [Co(**P6**)].

In an effort to directly trap α-Co(III)-heterobenzyl radical intermediate **I**, the metalloradical activation of 3-pyridyldiazomethane (**1b'**) by [Co(**P1**)] was carried out in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) without alkene substrates, resulting in the isolation of bis-TEMPO-trapped product **4** in 19% yield (Scheme 3B). The observation of compound **4** evidently implies the initial formation of α-Co(III)-pyridyl radical $\mathbf{I}_{1b}$, which was presumably captured by TEMPO through radical recombination to generate Co(III)-alkyl intermediate $\mathbf{III}_{1b}$. Subsequent radical substitution reaction of intermediate $\mathbf{III}_{1b}$ with a second molecule of TEMPO was likely responsible for the final formation of **4**. Similarly, bis-TEMPO-trapped product **5** was isolated in 12% yield from the metalloradical activation of 3-quinolinyldiazomethane (**1g'**) by [Co(**P1**)] in the presence of TEMPO, indicating the existence of α-Co(III)-heterobenzyl radical

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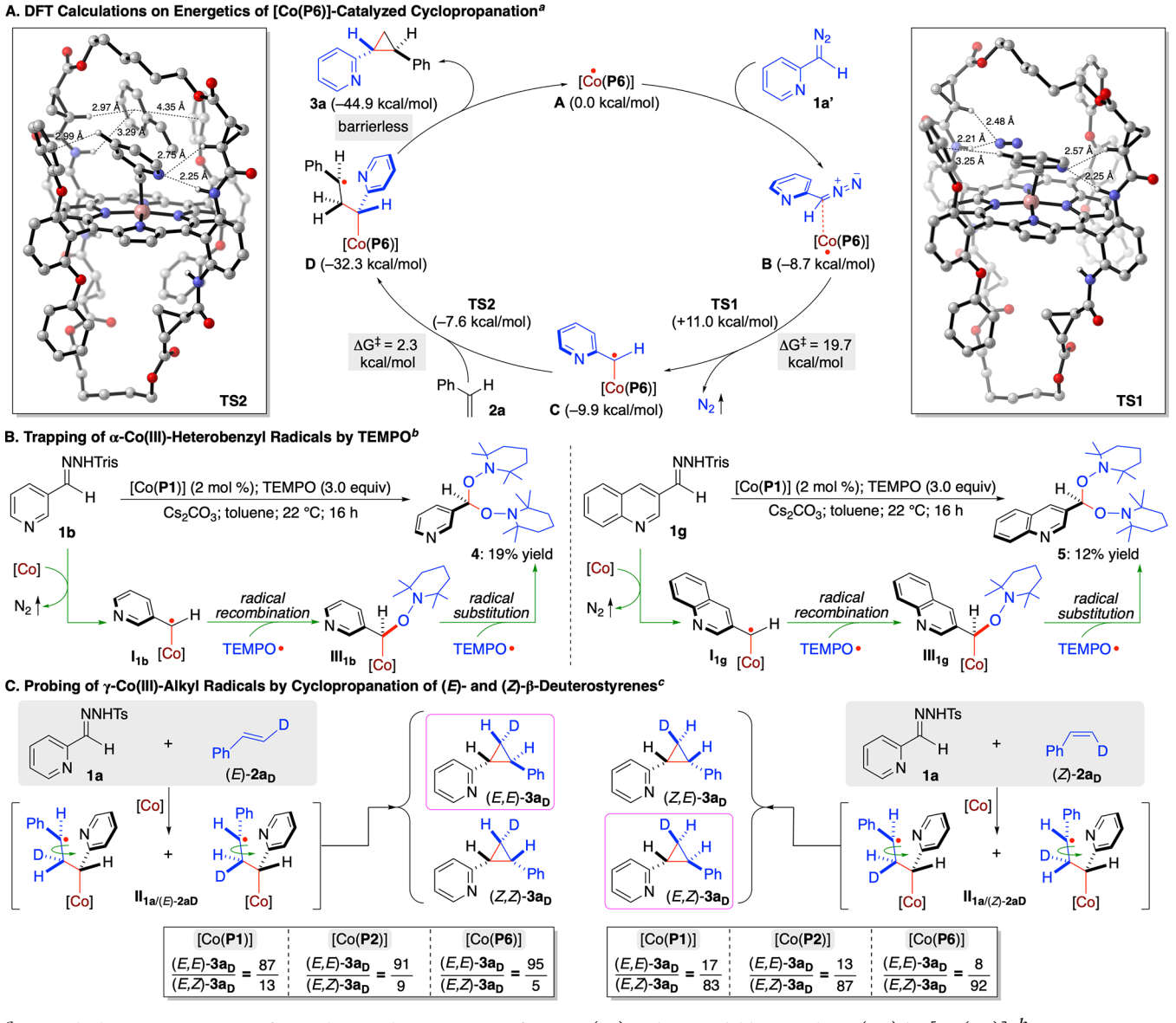
Scheme 3. Mechanistic Studies on Co(II)-Catalyzed Radical Olefin Cyclopropanation with Heteroaryldiazomethanes[a,b,c]



[a]DFT calculations on energetics for catalytic cyclopropanation of styrene (**2a**) with 2-pyridyldiazomethane (**1a'**) by [Co(**P6**)]. [b]TEMPO-trapping experiments for metalloradical activation of 3-pyridyl trishydrazone (**1b**) and 3-quinolinyl trishydrazone (**1g**) by [Co(**P1**)]. [c]Catalytic cyclopropanation reactions of (*E*)- and (*Z*)-*β*-deuterostyrenes with 2-pyridyl tosylhydrazone (**1a**) by [Co(**P1**)], [Co(**P2**)], and [Co(**P6**)].

intermediate $\mathbf{I}_{1g}$ and the following Co(III)-alkyl intermediate $\mathbf{III}_{1g}$ (Scheme 3B).

To probe the involvement of the *γ*-Co(III)-alkyl radical intermediate **II** in the proposed mechanism (Scheme 1), both isotopomers of *β*-deuterostyrene (*E*)-$\mathbf{2a}_D$ and (*Z*)-$\mathbf{2a}_D$ were employed as substrates for Co(II)-catalyzed cyclopropanation with 2-pyridyl tosylhydrazone (**1a**). Unlike a concerted mechanism that results in stereospecific cyclopropane products, a stepwise radical mechanism may give rise to the formation of four possible diastereomers of cyclopropanes due to the potential rotation of the *β*-C−C bond in *γ*-Co(III)-alkyl radicalintermediate **II** before cyclization. As expected, both reactions of (*E*)-$\mathbf{2a}_D$ and (*Z*)-$\mathbf{2a}_D$ with **1a** afforded the cyclopropane products as a mixture of four different diastereomers: (*E*,*E*)-$\mathbf{3a}_D$, (*Z*,*Z*)-$\mathbf{3a}_D$, (*Z*,*E*)-$\mathbf{3a}_D$, and (*E*,*Z*)-$\mathbf{3a}_D$ (Scheme 3C; see Supporting Information for details). Among them, the ratio between isotopomers (*E*,*E*)-$\mathbf{3a}_D$ and (*E*,*Z*)-$\mathbf{3a}_D$ could be accurately determined by the combination of ^{1}H and ^{2}H NMR analysis. When the bridged [Co(**P6**)] was used as the catalyst, the isotopomeric ratio of (*E*,*E*)-$\mathbf{3a}_D$ to (*E*,*Z*)-$\mathbf{3a}_D$ was determined to be 95:5 and 8:92 for the cyclopropanation reactions of (*E*)-$\mathbf{2a}_D$ and (*Z*)-$\mathbf{2a}_D$, respectively. This observation of both (*E*)- and (*Z*)-isotopomers of (*E*)-**3a** in both reactions evidently suggested the rotation of *β*-C−C bond in the corresponding *γ*-Co(III)-alkyl radical intermediates $\mathbf{II}_{1a/(E)\text{-}2aD}$ and $\mathbf{II}_{1a/(Z)\text{-}2aD}$. When the nonbridged [Co(**P2**)] was employed as the catalyst, the isotopomeric ratio of (*E*,*E*)-$\mathbf{3a}_D$ to (*E*,*Z*)-$\mathbf{3a}_D$ changed for both reactions of (*E*)-$\mathbf{2a}_D$ (from 95:5 to 91:9) and (*Z*)-$\mathbf{2a}_D$ (from 8:92 to 13:87), indicating a higher degree of the *β*-C−C bond rotation in the less-hindered catalyst environment. Accordingly, the use of even less-hindered catalyst [Co(**P1**)] allowed a further increase in the degree of the *β*-C−C bond rotation, changing the isotopomeric ratio of (*E*,*E*)-$\mathbf{3a}_D$ to (*E*,*Z*)-$\mathbf{3a}_D$ to 87:13 and

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17:83, respectively, for the two reactions. Collectively, these experimental results, together with the DFT calculations, provided corroborating evidence for the proposed stepwise radical mechanism of the Co(II)-catalyzed asymmetric cyclopropanation with heteroaryldiazomethanes.

CONCLUSIONS

In summary, we have applied Co(II)-based metalloradical catalysis (MRC) for the successful development of asymmetric radical cyclopropanation of alkenes with heteroaryldiazomethanes. With the newly synthesized bridged D_2-symmetric chiral amidoporphyrin 2,6-DiPhO-Hu(C_6)Phyrin as the optimal supporting ligand, the Co(II)-based metalloradical system can effectively activate different types of heteroaryldiazomethanes even at room temperature for olefin cyclopropanation, offering a general approach for stereoselective synthesis of chiral heteroaryl cyclopropanes. In addition to styrene derivatives, the Co(II)-catalyzed cyclopropanation is highlighted by an extraordinarily broad scope of alkenes, including several types of challenging substrates, affording a diverse range of heteroaryl cyclopropanes in high yields with excellent both diastereoselectivities and enantioselectivities. Furthermore, our combined computational and experimental studies have provided several lines of evidence in elucidating the underlying stepwise radical mechanism of the Co(II)-based olefin cyclopropanation involving α- and γ-metalloalkyl radicals as the key intermediates. In view of the ubiquity of the resulting enantioenriched heteroaryl cyclopropanes in biologically important compounds, we hope this Co(II)-catalyzed asymmetric radical cyclopropanation process will find wide applications in organic synthesis related to drug discovery.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04655.

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

Accession Codes

CCDC 2083336−2083339 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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