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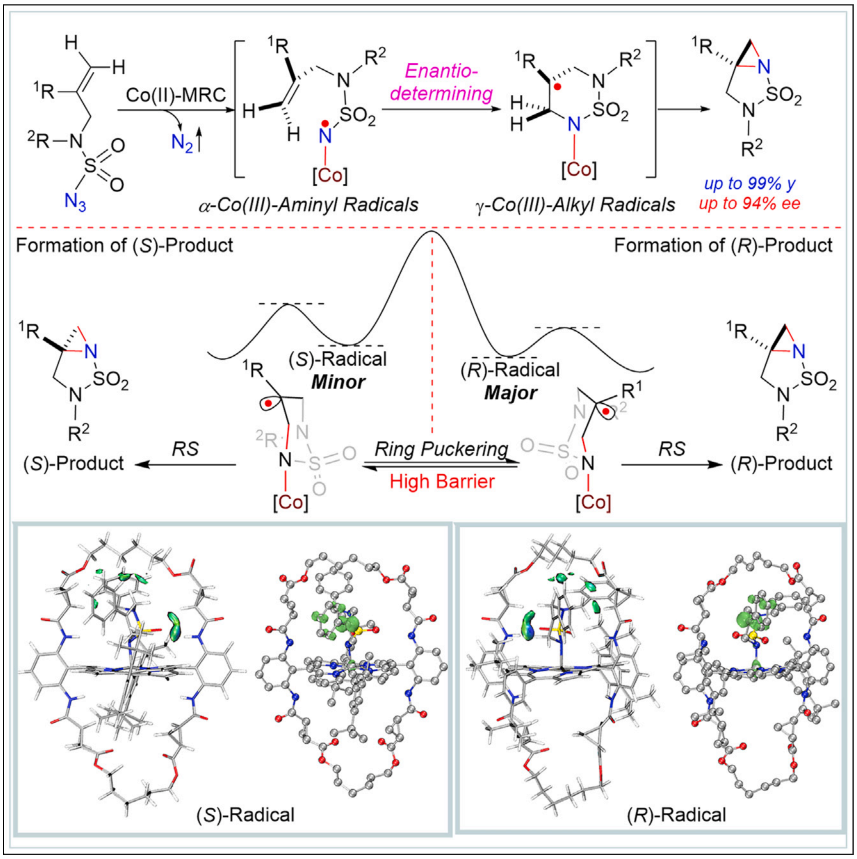

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Highlights

Catalytic *N*-heterobicyclization for the asymmetric synthesis of bicyclic aziridines

Importance of ligand design in developing Co(II)-based metalloradical catalysis

Detailed mechanistic elucidation of enantioselective radical *N*-heterobicyclization

New mode of asymmetric induction involving kinetically stable chiral radical center

The first catalytic system for enantioselective radical *N*-heterobicyclization of *N*-allylsulfamoyl azides has been developed via Co(II)-based metalloradical catalysis (MRC), allowing for the stereoselective construction of chiral [3.1.0]-bicyclic sulfamoyl aziridines in excellent yields with high diastereoselectivities and enantioselectivities. Comprehensive experimental and computational investigations have unveiled a new mode of asymmetric induction in radical chemistry that involves a radical intermediate bearing kinetically stable chiral radical center. The key to achieving high control of this uncommon enantioface-selectivity relies on catalyst development through ligand design.

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New mode of asymmetric induction for enantioselective radical *N*-heterobicyclization via kinetically stable chiral radical center

Hao Xu,[1] Duo-Sheng Wang,[1] Zhenyu Zhu,[1] Arghya Deb,[1] and X. Peter Zhang[1,2,*]

SUMMARY

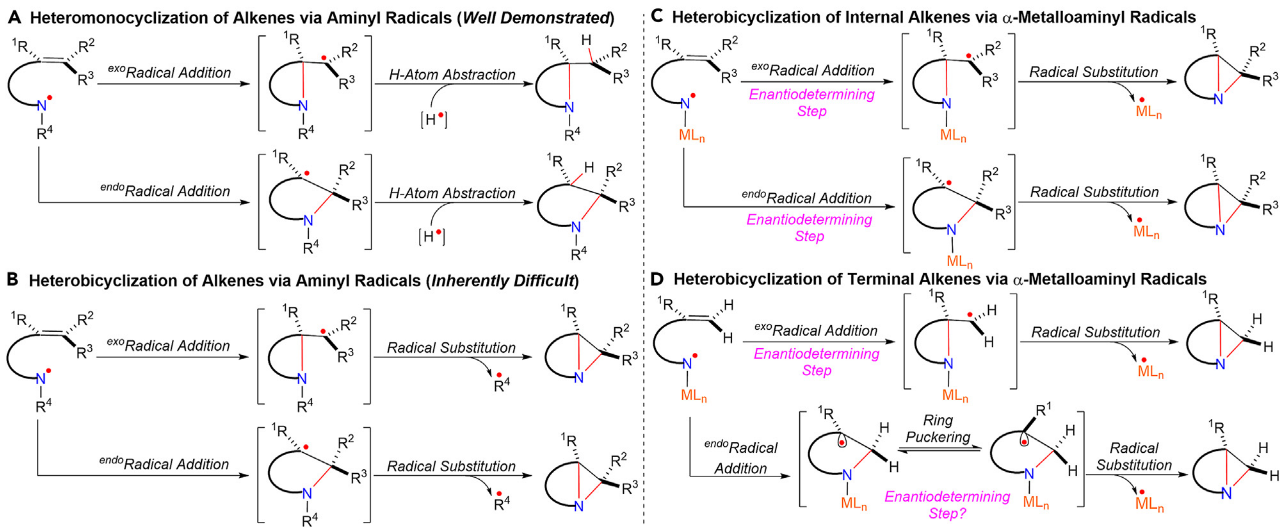
Enantioselective radical *N*-heterobicyclization of *N*-allylsulfamoyl azides has been developed via metalloradical catalysis (MRC). The Co(II)-based catalytic system can homolytically activate the organic azides with varied electronic and steric properties for asymmetric radical *N*-heterobicyclization under mild conditions without the need of oxidants, allowing for the stereoselective construction of chiral [3.1.0]-bicyclic sulfamoyl aziridines in excellent yields with high diastereoselectivities and enantioselectivities. The key to achieving the enantioselective radical process relies on catalyst development through ligand design. We demonstrate that the use of new-generation D_2-symmetric chiral bridged amidoporphyrin ligand HuPhyrin with judicious variation of the alkyl bridge length can dictate both the reactivity and selectivity of Co(II)-based MRC. We present both experimental and computational studies that shed light on the working details of the unprecedented mode of asymmetric induction consisting of enantioface-selective radical addition (RA) and stereospecific radical substitution (RS). We showcase the synthetic applications of the resulting enantioenriched bicyclic aziridines through a number of stereospecific transformations.

INTRODUCTION

Growing efforts have been devoted to utilizing aminyl radicals as versatile intermediates for constructing nitrogen-containing organic compounds.[1–5] Nitrogen-centered radicals have been widely used for intramolecular radical heterocyclization, constructing *N*-heterocyclic structures. Although previous studies mainly focused on the *N*-heteromonocyclization of free aminyl radicals involving intramolecular radical addition (RA) to an alkene unit and subsequent termination of the initially formed alkyl radical intermediate by intermolecular radical reactions, such as H-atom abstraction (HAA) (Scheme 1A),[6,7] a potential *N*-heterobicyclization through intramolecular radical substitution (RS) at the original nitrogen center has been less explored due to the challenges of homolytic RS at a tertiary nitrogen center by alkyl radicals, which requires a highly organized and sterically demanding transition state (Scheme 1B). One potential solution would be replacing free aminyl radicals $R(R^4)N\cdot$ with α-metalloaminyl radicals $R(L_nM)N\cdot$, where the alkyl group R^4 is substituted by metal complex L_nM (Scheme 1C). The substitution allows for facile RS due to weaker M–N bond and the use of stable metalloradicals $L_nM\cdot$ as good radicofuges.[8–12] Furthermore, if α-metalloaminyl radicals could be generated from the metalloradical activation (MRA) of nitrogen compounds, this *N*-heterobicyclization process based on the RA-RS pathway could proceed in a catalytic fashion while enabling the possibility for the asymmetric synthesis of *N*-heterobicyclic structures when chiral

THE BIGGER PICTURE

Controlling enantioselectivity and reactivity remains a major challenge in radical chemistry. The advancement of metalloradical catalysis (MRC) strives to address this issue in a fundamentally different approach, allowing for catalytic asymmetric radical transformations. With D_2-symmetric chiral amidoporphyrins as the ligand platform, Co(II)-based MRC exhibits unusual ability to govern stereochemical course of radical reactions in achieving fine control of reactivity and stereoselectivity while affording ground to uncover new modes of asymmetric induction for forging stereocenters. As showcased with asymmetric radical *N*-heterobicyclization of allylic sulfamoyl azides, we reveal a new mode of asymmetric induction that involves 6-*endo-trig* addition of initially formed α-Co(III)-aminyl radical to terminal olefin. The resulting γ-Co(III)-alkyl radical intermediate, which bears a kinetically stable chiral radical center, undergoes stereospecific annulation via 3-*exo-tet* radical cyclization.



Scheme 1. Monocyclization and bicyclization of aminyl radicals for the construction of *N*-heterocyclic structures

metalloradicals $^*L_nM\cdot$ are employed. In the case of asymmetric *N*-heterobicyclization of internal alkenes, enantioselectivity would be determined by the first step of RA, regardless of the *endo*- or *exo*-fashion addition of the α-metalloaminyl radical to the alkene unit (Scheme 1C). For *exo*-addition to terminal alkenes, the first step of RA should be enantiodetermining, whereas for endo-addition, either the first step of RA or the second step of RS could control asymmetric induction, depending on the kinetic stability of the initially generated chiral radical center on the ring as illustrated (Scheme 1D).

Homolytic radical chemistry has been increasingly pursued for the development of new synthetic strategies to construct organic molecules.[13–17] However, the ongoing endeavor has faced several challenges, including the particular issue of controlling enantioselectivity.[18–20] Among recent advances in addressing these challenges,[21–32] metalloradical catalysis (MRC) offers a conceptually different approach that is based on the catalytic generation of metal-stabilized organic radicals as key intermediates upon the MRA of radical precursors (metalloradicophiles) and further control of the subsequent homolytic radical reactions.[33–37] As stable 15e-metalloradicals, Co(II) complexes of porphyrins have an unusual capability of homolytically activating organic azides to generate α-Co(III)-aminyl radicals that can function as kinetically competent intermediates for catalytic radical transformations.[11,38–44] With the introduction of D_2-symmetric chiral amidoporphyrins as a versatile ligand platform, Co(II)-based MRC has been successfully applied for the asymmetric construction of 5- and 6-membered *N*-heteromonocyclic sulfamides via enantioselective 1,5- and 1,6-C–H amination of sulfamoyl azides, respectively.[45–49] The metalloradical processes involve the intramolecular HAA of C(sp^3)–H bonds by the initially generated α-Co(III)-aminyl radical intermediates, followed by the intramolecular RS of the resulting distal ω-Co(III)-alkyl radicals at the original nitrogen center to close the cyclic structures through C–N bond formation. Although Co(II)-MRC was also applied for the construction of *N*-heterobicyclic sulfamides from the intramolecular aziridination of allylic sulfamoyl azides,[50] our previous catalytic system was limited with the substrate scope and failed to address the issue of enantioselectivity. In light of the recent availability of new-generation bridged D_2-symmetric chiral amidoporphyrins,[51] we hoped to develop an asymmetric variant of the Co(II)-based catalytic process for the radical *N*-heterobicyclization of allylic sulfamoyl azides **1** to

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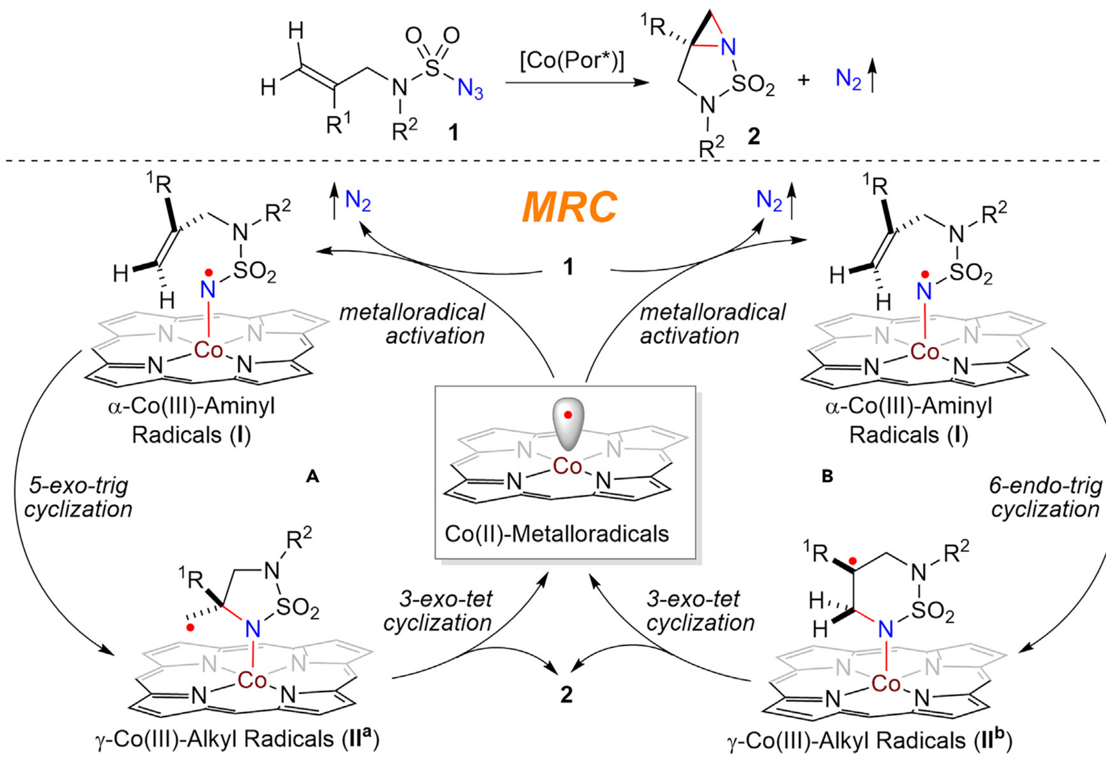


Scheme 2. Two potential catalytic pathways for the *N*-heterobicyclization of allylic sulfamoyl azides via Co(II)-MRC

stereoselectively construct highly strained chiral [3.1.0]-aziridines **2** (Scheme 2). Mechanistically, there are two potential catalytic pathways for radical *N*-heterobicyclization involving the initially generated α-Co(III)-aminyl radical intermediate I from the MRA of allylic sulfamoyl azides **1**. If intermediate I undergoes RA by 5-*exo-trig* cyclization (Scheme 2A), it delivers 5-membered γ-Co(III)-alkyl radical intermediate II^a with the generation of a stereogenic center. Subsequent RS of the primary radical intermediate II^a by 3-*exo-tet* cyclization leads to the fusion of a new 3-membered ring onto the pre-formed 5-membered structure for the production of bicyclic aziridines **2**. On the other hand, if the RA of intermediate I prefers 6-*endo-trig* cyclization (Scheme 2B), 6-membered γ-Co(III)-alkyl radical intermediate II^b will be formed with the generation of a pro-stereogenic radical center. In order to produce bicyclic aziridines **2**, the 6-membered ring in intermediate II^b will undergo ring annulation by 3-*exo-tet* cyclization through RS. Evidently, regioselectivity in the RA of α-Co(III)-aminyl radical intermediate I would shape the mode of asymmetric induction and could, in turn, impact the control of enantioselectivity for the catalytic process. Although 5-*exo-trig* radical cyclization of intermediate I clearly determines the enantioselectivity in catalytic pathway A, the enantiodetermining step in catalytic pathway B could be either 6-*endo-trig* radical cyclization of intermediate I or 3-*exo-tet* radical cyclization of intermediate II^b, depending on the kinetic stability of the 6-membered chiral radical center in intermediate II^b. If the stereoconfiguration of the prochiral radical center is kinetically labile similar to that of typical alkyl radicals, the final step of RS is expected to determine the enantioselectivity for the formation of bicyclic aziridines **2**. In an uncommon case where the stereoconfiguration of the prochiral radical center on the 6-membered ring is kinetically stable relative to the rate of the following RS, the enantioface-selectivity for the formation of γ-Co(III)-alkyl radical intermediate II^b via endo-addition to the terminal alkene in radical intermediate I is anticipated to determine the enantioselectivity of the overall catalytic process. To the best of our knowledge, this fundamental mode of asymmetric induction has not been previously documented. It was open to question whether high enantioselectivity could be achieved through this uncommon mode of asymmetric induction. We envisioned the possibility of assessing this appealing issue by fine-tuning the D_2-symmetric chiral amidoporphyrin ligand to adopt a proper steric, electronic, and chiral environment to govern the stereochemical course of Co(II)-based metalloradical system. If successfully achieved, this type of asymmetric radical *N*-heterobicyclization would be highly useful, as the resulting *N*-heterobicyclic structures can serve as versatile chiral building blocks for the stereoselective synthesis of functionalized vicinal diamines, which are common motifs in medicinally important compounds (Figure S1).

Catalytic asymmetric intramolecular aziridination of alkenes provides an attractive approach to the stereoselective construction of bicyclic aziridines through double C–N bond formation.[52–56] Although there were a number of reports on catalytic intramolecular olefin aziridination, the development of asymmetric catalytic systems for the stereoselective synthesis of chiral *N*-heterobicyclic aziridines has been limited.[57–63] Although the enantioselective intramolecular aziridination of sulfonamides, sulfamates, and carbamates have been reported to access bicyclic sulfonyl and carbonyl aziridines, the synthesis of more strained chiral [3.1.0]-bicyclic sulfamoyl aziridines is a challenging problem that remains unsolved. Although Co(II)-MRC was previously applied for the synthesis of [3.1.0]-bicyclic sulfamoyl aziridines in racemic forms,[50] it would be desirable to develop an asymmetric variant of the catalytic process for the enantioselective synthesis of chiral [3.1.0]-bicyclic sulfamoyl aziridines. Compared with the unstable [3.1.0]-bicyclic alkoxycarbonyl aziridines obtained from the asymmetric radical bicyclization of allyl azidoformates,[61] the [3.1.0]-bicyclic sulfamoyl aziridines, despite their higher strain, can be isolated as stable compounds,[50] making them synthetically more appealing. As part of our ongoing efforts in applying Co(II)-MRC for stereoselective organic synthesis, we herein report the development of the first catalytic system that is highly effective for the asymmetric *N*-heterobicyclization of *N*-allylsulfamoyl azides to construct chiral [3.1.0]-bicyclic sulfamoyl aziridines. Supported by a new-generation D_2-symmetric chiral amidoporphyrin ligand, the Co(II)-based metalloradical system, which features operational simplicity and mild conditions without the need of oxidants or any additive, can activate *N*-allylsulfamoyl azides with varied electronic and steric properties to enable the stereoselective construction of chiral [3.1.0]-bicyclic sulfamoyl aziridines. Through the fine-tuning of the ligand environment, we show the significance of catalyst evolution in achieving high reactivity and stereoselectivity for this new stereoselective radical process. Mechanistically, we present comprehensive experimental and computational investigations that allow us to examine the working details of the underlying stepwise radical pathway of the Co(II)-based metalloradical system, including the uncovering of an unprecedented mode of asymmetric induction. Furthermore, we showcase the synthetic applications of the Co(II)-catalyzed asymmetric *N*-heterobicyclization through a series of stereospecific transformations of the resulting enantioenriched [3.1.0]-bicyclic sulfamoyl aziridines.

RESULTS AND DISCUSSION

Reaction development

At the outset of this project, *N*-benzyl-*N*-allylsulfamoyl azide **1a** was selected as a model substrate to explore the proposed asymmetric *N*-heterobicyclization by Co(II)-based metalloradical catalysts (Figure 1). It was found that first-generation

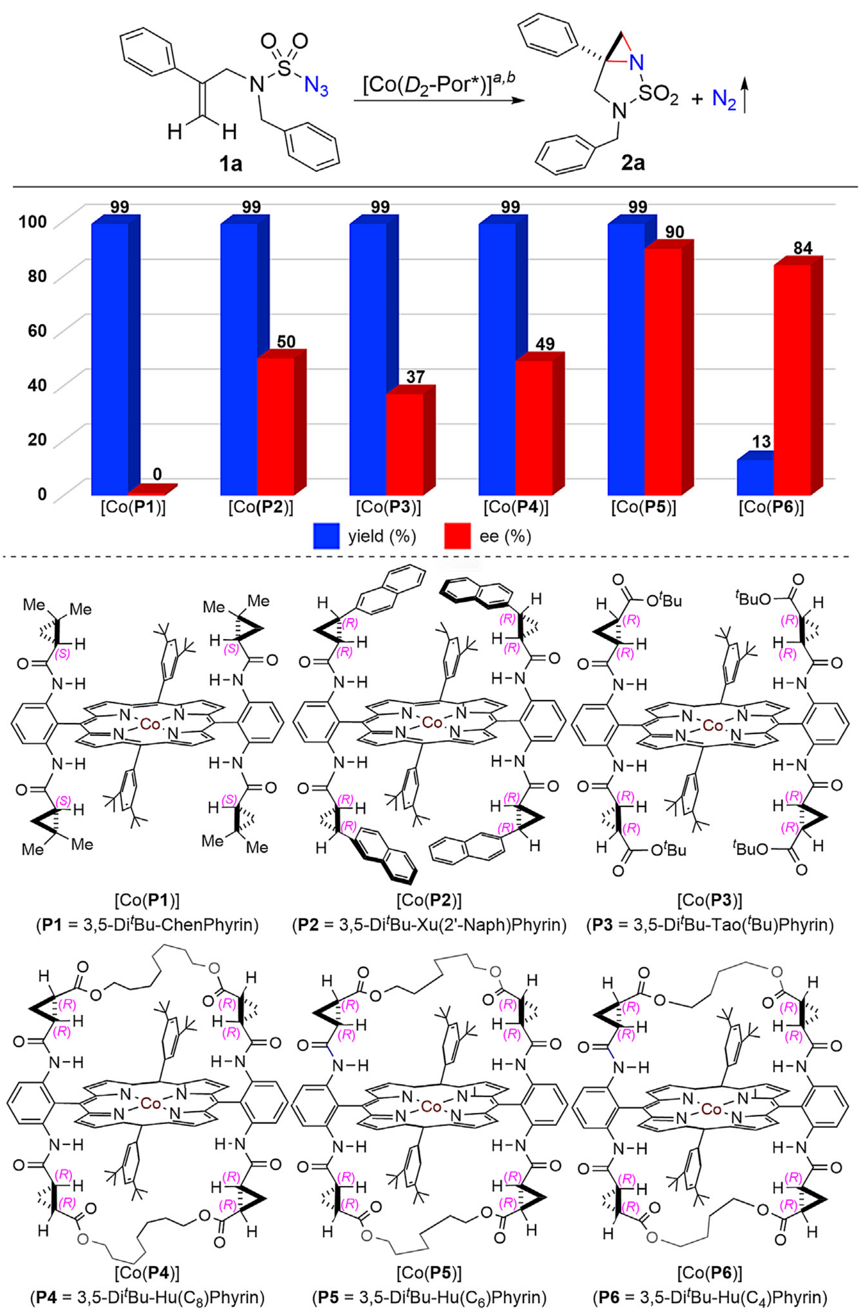


Figure 1. Ligand effect on Co(II)-based catalytic system for the asymmetric bicyclization of *N*-allylsulfamoyl azide

[a]Performed in toluene at 40°C for 14 h using [Co(Por*)] (3 mol %) under N_2 in the presence of 4 Å molecular sieves (MS); [**1a**] = 0.2 M.

[b]NMR yields; enantiomeric excess (ee) determined by chiral high-performance liquid chromatography (HPLC).

metalloradical catalyst [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-ChenPhyrin)[64] could effectively catalyze the *N*-heterobicyclization reaction of azide **1a**, affording the desired [3.1.0]-bicyclic aziridine **2a** in an excellent yield (99%) but without any observable asymmetric induction. When second-generation metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-Xu(2′-Naph)Phyrin)[65] with 2-naphthyl substituents on the chiral amide units was used, significant enantioselectivity (50% enantiomeric excess [ee]) was observed for the formation of **2a** without affecting the excellent yield. However, changing the catalyst to [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-Tao(^{t}Bu)Phyrin),[51] another second-generation metalloradical catalyst that bears chiral amide units with ester groups, caused a decrease in enantioselectivity (37% ee) for the *N*-heterobicyclization reaction but with no negative effect on the excellent yield. To improve the enantioselectivity of the catalytic transformation, we then turned our attention to new-generation metalloradical catalysts [Co(HuPhyrin)], the Co(II) complexes of bridged D_2-symmetric chiral amidoporphyrins that are derived from [Co(**P3**)] with alkyl bridges across two chiral amide units on both sides of the porphyrin plane and feature more rigid cavity-like environments.[51] When [Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-Hu(C_8)Phyrin) with C_8-bridged alkyl chains was employed as the catalyst, it was found that aziridine **2a** could be generated with better enantioselectivity than [Co(**P3**)] (49% vs. 37% ee) while retaining the excellent yield (99%). To our delight, switching the catalyst [Co(**P4**)] to [Co(**P5**)] (**P5** = 3,5-Di^{t}Bu-Hu(C_6)Phyrin) bearing a shorter C_6-alkyl bridge gave rise to a dramatic enhancement of enantioselectivity from 49% to 90% ee for the formation of aziridine **2a** without adverse influence on the outstanding yield (99%). Interestingly, when the alkyl bridge of HuPhyrin ligand was further shortened, it led to substantial reduction in reactivity as well as a noticeable decrease in the enantioselectivity of the Co(II)-catalyzed reaction as shown for the bicyclization of azide **1a** by C_4-bridged [Co(**P6**)] (**P6** = 3,5-Di^{t}Bu-Hu(C_4)Phyrin), giving aziridine **2a** in only 13% yield with 84% ee. This reversed outcome is likely attributed to the overly tight cavity environment of catalyst [Co(**P6**)] as a result of the significantly shorter C_4-alkyl bridge. Altogether, these results demonstrate a remarkable ligand effect on both the catalytic reactivity and product enantioselectivity of asymmetric radical bicyclization in Co(II)-based metalloradical system (Figure 1).

Substrate scope

Under the optimized conditions, the substrate scope and versatility of [Co(**P5**)]-catalyzed asymmetric *N*-heterobicyclization were evaluated with sulfamoyl azides **1** containing various alkene functionalities (Figure 2). Similar to *N*-benzyl-*N*-allylsulfamoyl azide **1a** (Figure 2; entry 1), its derivatives possessing both electron-donating and electron-withdrawing aryl substituents, including 4-Me (**1b**), 3,5-di-Me (**1c**), 4-MeO (**1d**), 4-Cl (**1e**), 4-Br (**1f**), 2-F (**1g**), 3,5-di-F (**1h**), 4-CF_3 (**1i**), and 4-CN (**1j**), could be effectively bicyclized by [Co(**P5**)], affording the desired [3.1.0]-bicyclic sulfamoyl aziridines **2b–2j** in excellent yields with comparatively high enantioselectivities (Figure 2; entries 2–10). The absolute configuration of the major enantiomers of both **2i** and **2j** were established as (*R*). It is worth mentioning that the catalytic *N*-heterobicyclization process could be readily scaled up as demonstrated with the bicyclization reaction of **1a** on 1.0 mmol scale, delivering highly enantioenriched compound (–)-**2a** in 96% yield with 90% ee (Figure 2; entry 1). Substrates containing functional groups, such as ester (**1k**), ether (**1l**), amine (**1m**), and borate (**1n**), were found compatible with the current catalytic system, leading to the desired products **2k–2n** in moderate to high yields with high enantioselectivities (Figure 2; entries 11–14). Furthermore, the [Co(**P5**)]-catalyzed *N*-heterobicyclization system was shown to be effective with substrates bearing extended arenes and heteroarenes, such as naphthalene (**1o**), benzothiophene (**1p**), thiophene (**1q**), furan (**1r**), 2,3-dihydrobenzofuran (**1s**), 1,3-benzodioxole (**1t**), and 1,4-benzodioxan (**1u**), allowing for the asymmetric construction of [3.1.0]-bicyclic sulfamoyl aziridines **2o–2u** in excellent yields with high enantioselectivities (Figure 2; entries 15–21). Interestingly, the [Co(**P5**)]-based system could efficiently catalyze the bicyclization reaction of substrate **1v** bearing the phosphonate unit, delivering **2v** in a high yield albeit with poor enantioselectivity

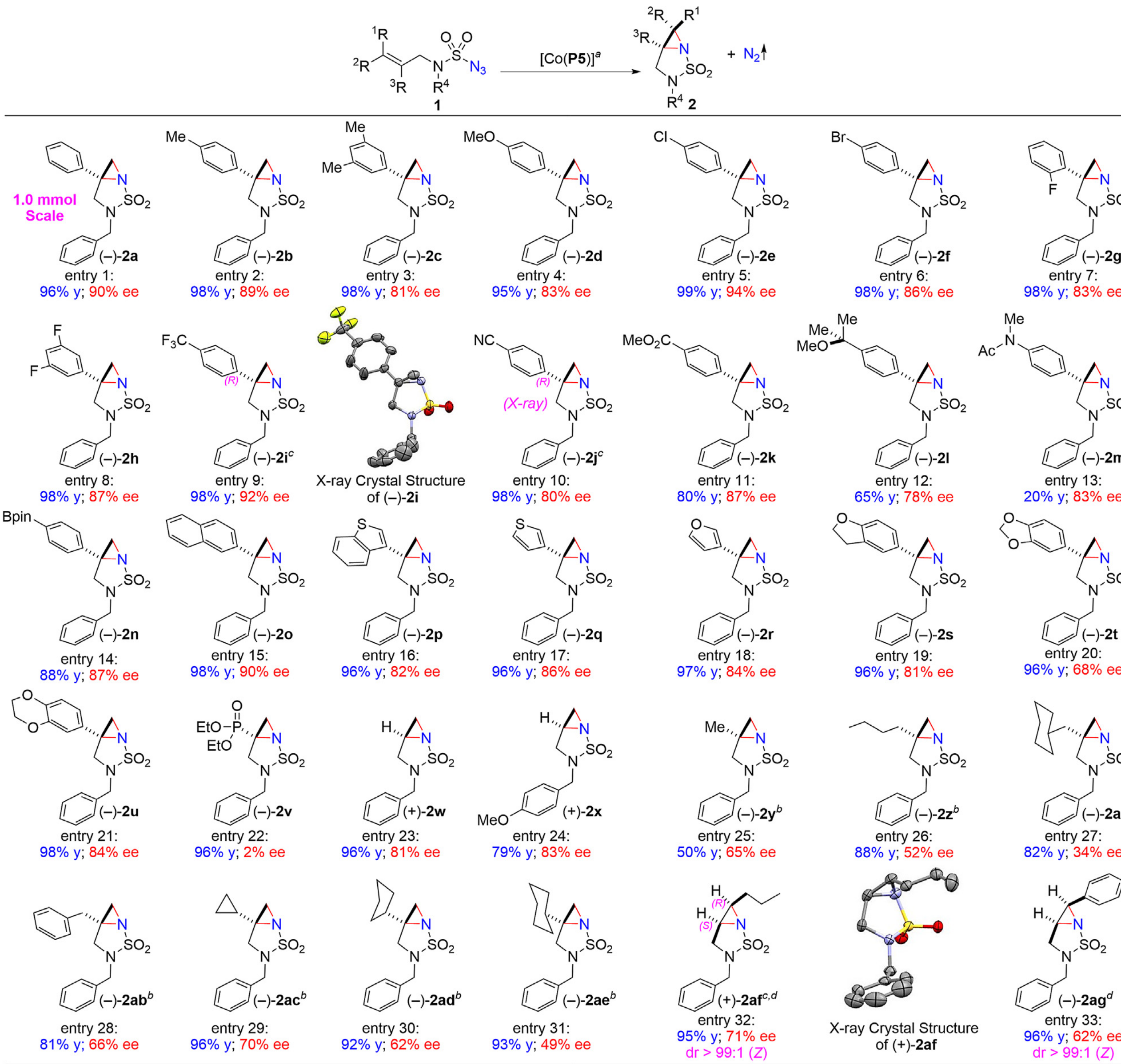


Figure 2. Substrate scope of the Co(II)-catalyzed asymmetric intramolecular radical bicyclization of allylic sulfamoyl azides

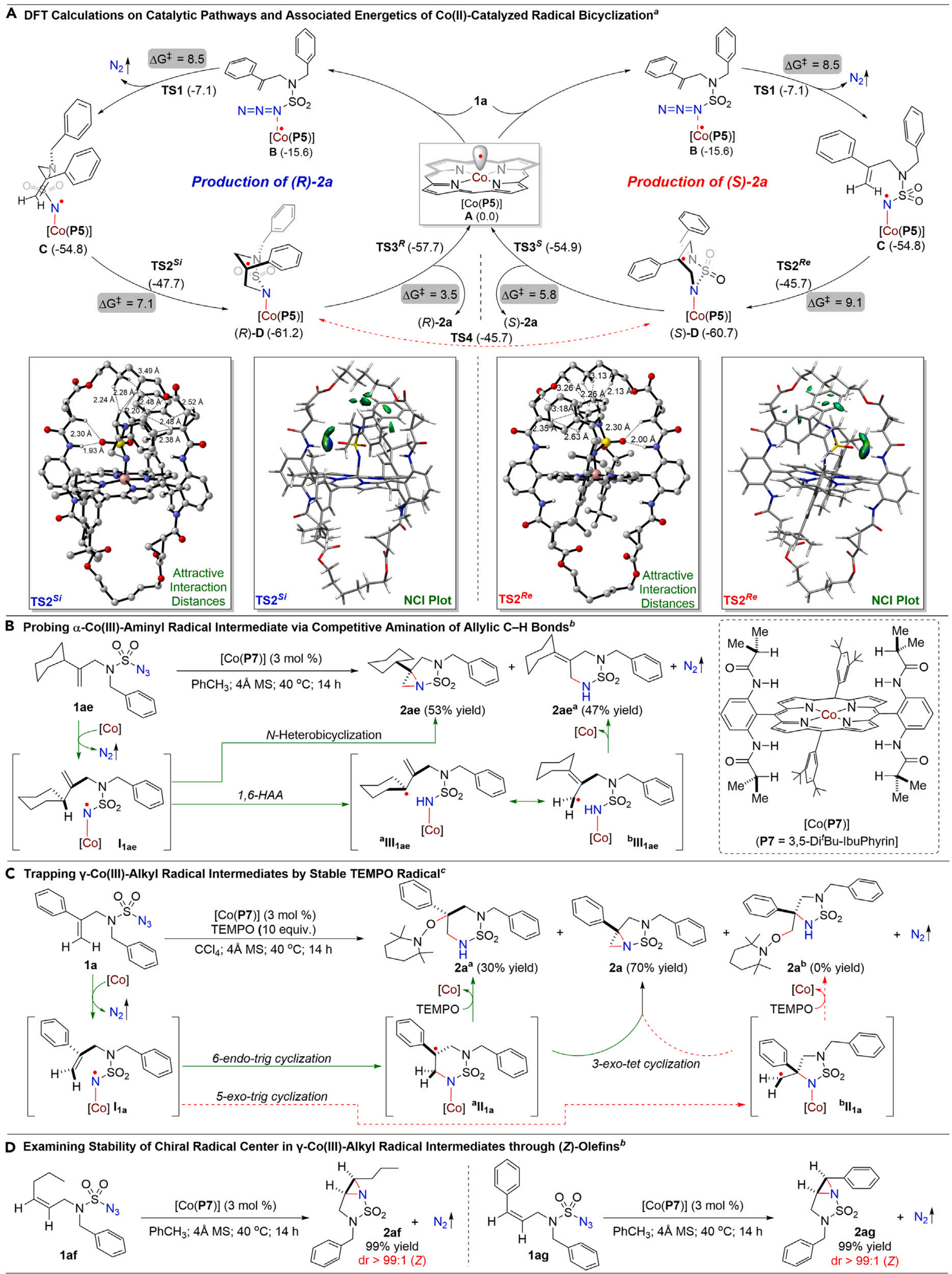
[a]Performed in toluene at 40°C for 14 h using [Co(**P5**)] (3 mol %) under N_2 in the presence of 4 Å MS; [**1**] = 0.2 M; isolated yields; enantiomeric excess (ee) determined by chiral HPLC.

[b]Performed in cyclohexane.

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

[d]From corresponding (*Z*)-olefins.

(Figure 2; entry 22). It should be emphasized that the [Co(**P5**)]-catalyzed *N*-heterobicyclization system is not confined to *N*-allylsulfamoyl azides containing electronically activated alkenes. Notably, the catalytic system proved to be similarly effective for the asymmetric heterobicyclization of *N*-allylsulfamoyl azides with nonactivated aliphatic alkenes, such as monosubstituted olefins (**1w** and **1x**) and disubstituted olefins carrying various alkyl groups (**1y–1ae**), leading to the successful construction of [3.1.0]-bicyclic sulfamoyl aziridines **2w–2ae** in good to excellent yields with moderate to good enantioselectivities (Figure 2; entries 23–31). Previously, Co(II)-based


A DFT Calculations on Catalytic Pathways and Associated Energetics of Co(II)-Catalyzed Radical Bicyclization[a]
Production of (R)-2a
Production of (S)-2a
1a
[Co(P5)]
A (0.0)
B (-15.6)
C (-54.8)
TS1 (-7.1)
ΔG‡ = 8.5
TS2^Si (-47.7)
ΔG‡ = 7.1
TS2^Re (-45.7)
ΔG‡ = 9.1
(R)-D (-61.2)
(S)-D (-60.7)
TS3^R (-57.7)
TS3^S (-54.9)
ΔG‡ = 3.5
ΔG‡ = 5.8
(R)-2a
(S)-2a
TS4 (-45.7)
Attractive Interaction Distances
NCI Plot
B Probing α-Co(III)-Aminyl Radical Intermediate via Competitive Amination of Allylic C–H Bonds[b]
[Co(P7)] (3 mol %)
PhCH3; 4Å MS; 40 °C; 14 h
1ae
2ae (53% yield)
2ae^a (47% yield)
N-Heterobicyclization
1,6-HAA
I1ae
aIII1ae
bIII1ae
[Co(P7)]
(P7 = 3,5-Di^tBu-IbuPhyrin)
C Trapping γ-Co(III)-Alkyl Radical Intermediates by Stable TEMPO Radical[c]
[Co(P7)] (3 mol %)
TEMPO (10 equiv.)
CCl4; 4Å MS; 40 °C; 14 h
1a
2a^a (30% yield)
2a (70% yield)
2a^b (0% yield)
6-endo-trig cyclization
5-exo-trig cyclization
3-exo-tet cyclization
I1a
aII1a
bII1a
D Examining Stability of Chiral Radical Center in γ-Co(III)-Alkyl Radical Intermediates through (Z)-Olefins[b]
[Co(P7)] (3 mol %)
PhCH3; 4Å MS; 40 °C; 14 h
1af
2af
99% yield
dr > 99:1 (Z)
1ag
2ag
99% yield
dr > 99:1 (Z)

Scheme 3. Mechanistic studies on Co(II)-based metalloradical system for the *N*-heterobicyclization of allylic sulfamoyl azides

[a]Applied bp86/6-311G(d)/def2-svp for geometry optimization and bp86/6-311G(d)/def2-tzvp for energy calculations (kcal/mol) at 40°C along with Grimme's dispersion correction.

[b]Performed in toluene at 40°C for 14 h using [Co(**P7**)] (3 mol %) under N_2 in the presence of 4 Å MS; [**1**] = 0.2 M; NMR yields.

[c]Performed in carbon tetrachloride with TEMPO (10.0 equiv) at 40°C for 14 h using [Co(**P7**)] (3 mol %) under N_2 in the presence of 4 Å MS; [**1**] = 0.2 M; NMR yields.

metalloradical system was shown to catalyze the intramolecular amination of allylic C–H bonds.[66,67] It was shown that [Co(**P5**)]-based system could catalyze chemoselective reaction with the C=C bonds without affecting the allylic C–H bonds as exemplified by the formation of the desired [3.1.0]-bicyclic sulfamoyl aziridines **2y**–**2ae** in good yields with moderate enantioselectivities (Figure 2; entries 25–31). Furthermore, the catalytic radical *N*-heterobicyclization by [Co(**P5**)] was found to be effective even in catalyzing the radical bicyclization of *N*-allylsulfamoyl azides bearing internal alkenes as exemplified by the reactions of (*Z*)-**1af** and (*Z*)-**1ag** as the substrates, affording the corresponding (*Z*)-**2af** and (*Z*)-**2ag** in excellent yields with good enantioselectivities and complete preservation of the original (*Z*)-stereochemistry of the alkene units (Figure 2; entries 32 and 33). The absolute configurations of the major enantiomer of (*Z*)-**2af** were established as (*5S*,*6R*). It should be noted that the current catalytic system was found to be ineffective for *N*-allylsulfamoyl azides containing certain type of alkenes, including terminal alkenes with bulky substituents, trans-internal alkenes, and tri-substituted alkenes. This can be attributed to their steric hinderance (see supplemental information for details).

Mechanistic studies

Combined computational and experimental investigations were conducted to shed light on the underlying stepwise mechanism of the Co(II)-based catalytic system for asymmetric *N*-heterobicyclization, including the origin of regioselectivity and enantioselectivity (Scheme 3). First, density functional theory (DFT) calculations were performed to examine the details of the catalytic pathway and ascertain the origin of the asymmetric induction through elucidating the associated energetics of the asymmetric radical bicyclization process with *N*-benzyl-*N*-allylsulfamoyl azide **1a** by metalloradical catalyst [Co(**P5**)] (Scheme 3A; see Scheme S2 for more details). The DFT calculations reveal strong binding of azide **1a** by catalyst [Co(**P5**)] through the interplay of metal coordination, multiple H-bonding, and other non-covalent interactions to form the initial substrate complex **B**. This binding process is associated with a negative change of Gibbs free energy by 15.6 kcal/mol. Through these attractive forces, the α-nitrogen atom of sulfamoyl azide **1a** is positioned in close proximity to the Co(II)-metalloradical center of [Co(**P5**)] (N···Co: 2.129 Å) for advancing further interaction. The following MRA, which is highly exergonic by 39.2 kcal/mol, is associated with a readily accessible activation barrier ($\Delta G^{\ddagger}_{\mathbf{TS1}}$ = 8.5 kcal/mol), generating α-Co(III)-aminyl radical intermediate **C** upon the extrusion of dinitrogen as byproduct. Between the two potential pathways of intramolecular RA (Scheme 2), the DFT calculations indicate that radical intermediate **C** prefers 6-*endo-trig* cyclization via the 6-membered transition state (T.S.) substantially over 5-*exo-trig* cyclization via the 5-membered T.S. by 8.8 kcal/mol (see Scheme S1). To rationalize the enantioselectivity observed for the catalytic reaction, we then calculated the energetics associated with the RA step via the preferred 6-*endo-trig* cyclization to both *Re*- and *Si*-faces of the terminal alkene unit in intermediate **C**, which led to the formation of γ-Co(III)-alkyl radical intermediate (*S*)-**D** with pro-(*R*) chirality and γ-Co(III)-alkyl radical intermediate (*R*)-**D** with pro-(*S*) chirality, respectively (Scheme 3A). According to the DFT calculations, the RA of intermediate **C** via pro-(*S*) T.S. $\mathbf{TS2}^{Si}$ is favored over pro-(*R*) T.S. $\mathbf{TS2}^{Re}$ both kinetically ($\Delta G^{\ddagger}_{\mathbf{TS2}}{}^{Si}$ = 7.1 kcal/mol; $\Delta G^{\ddagger}_{\mathbf{TS2}}{}^{Re}$ = 9.1 kcal/mol) and thermodynamically ($\Delta G^{\circ}_{(R)\text{-}\mathbf{D}}$ = −6.4 kcal/mol; $\Delta G^{\circ}_{(S)\text{-}\mathbf{D}}$ = −5.9 kcal/mol). As illustrated in the DFT-optimized structures of **TS2**^{Si} and **TS2**^{Re} (Scheme 3A), there exist two-point N–H····O=S and C–H····O=S hydrogen-bonding interactions between one of the cyclopropanecarboxamide units in the catalyst and the sulfonyl group of the substrate as well as other non-covalent attractive interactions such as CH···π interactions and van der Waals attraction between the alkyl chain of the catalyst and the substrate. Moreover, the corresponding non-covalent interaction (NCI) plots apparently show the presence of stronger attractions in **TS2**^{Si} than in **TS2**^{Re}, which is contributed to the difference between the two activation barriers (Scheme 3A; see Scheme S4). Based on the DFT calculations, both intermediates (*S*)-**D** and (*R*)-**D** proceed the last step of ring annulation via 3-*exo-tet* radical cyclization readily, as judged by the low activation barriers ($\Delta G^{\ddagger}{}_{TS3}{}^{R}$ = 3.5 kcal/mol; $\Delta G^{\ddagger}{}_{TS3}{}^{S}$ = 5.8 kcal/mol), giving rise to the final product [3.1.0]-bicyclic sulfamoyl aziridine as (*R*)-**2a** and (*S*)-**2a** enantiomers, respectively. Additional calculations reveal that the interconversion between intermediates (*S*)-**D** and (*R*)-**D** through chair flipping (ring puckering) has a relatively high activation barrier ($\Delta G^{\ddagger}{}_{TS4} \approx$ 15 kcal/mol) due to the existence of multiple non-covalent attractive interactions (including H-bonding and π-stacking interactions) in the two intermediates (see Scheme S2). Consequently, intermediates (*S*)-**D** and (*R*)-**D**, without interconversion through the ring puckering, are expected to independently undergo the facile step of RS to deliver respective enantiomer of the final product while regenerating the Co(II)-metalloradical catalyst. Accordingly, it is concluded that the RA of α-Co(III)-aminyl radical intermediate **C** via 6-*endo-trig* cyclization is the enantiodetermining step, generating γ-Co(III)-alkyl radical intermediate **D** with the creation of a 6-membered chiral radical center that is kinetically stable without racemization before undergoing the succeeding ring annulation in a stereospecific manner. Quantitatively, the computed difference in activation barriers ($\Delta\Delta G^{\ddagger}{}_{TS2}$ = 2.0 kcal/mol) between **TS2**^{Re} and **TS2**^{Si} matches well with the observed enantioselectivity (90% ee) for [3.1.0]-bicyclic sulfamoyl aziridine **2a**. Interestingly, the DFT calculations indicate that the resulting aziridine **2a** binds strongly with catalyst [Co(**P5**)] through the interplay of metal coordination, multiple H-bonding, and other non-covalent interactions before it dissociates from the catalyst cavity to become the free product. The dissociation process is associated with a positive change of Gibbs free energy by 20.6 kcal/mol (see Scheme S2). Although the product binding is quite strong, the binding energy of 20.6 kcal/mol is not too strong to prevent the turnover of the catalytic process. Although the step of RA determines asymmetric induction, it is the dissociation of aziridine **2a** from catalyst [Co(**P5**)] that limits the overall rate of the catalytic process. Because the bicyclization of azide **1a** to form aziridine **2a** is highly exergonic due to the generation of the dinitrogen gas as the byproduct, the strong product binding should not inhibit the catalytic transformation.

Considerable efforts were made to experimentally probe and trap the key radical intermediates in the catalytic pathway as revealed by the computational studies for the Co(II)-based catalytic system for asymmetric *N*-heterobicyclization. As shown above (Figure 2; entry 31), *N*-allylsulfamoyl azide **1ae** bearing tertiary allylic C–H bonds at the cyclohexyl position could chemoselectively proceed the desired radical bicyclization under the catalysis of the optimal catalyst [Co(**P5**)], without any complication from the potentially competitive 1,6-C–H radical amination. However, when the achiral metalloradical catalyst [Co(**P7**)] (**P7** = 3,5-Di^{t}Bu-IbuPhyrin)[38] was applied for the reaction under the standard condition, a mixture of the bicyclization product **2ae** and C–H amination product **2ae^a** were obtained in 53% and 47% yield, respectively (Scheme 3B). The formation of **2ae^a** evidently implies the initial generation of α-Co(III)-aminyl radical intermediate $\mathbf{I_{1ae}}$ via MRA of azide **1ae** by [Co(**P7**)],[66,67] which undergoes 1,6-HAA to give ζ-Co(III)-allylic radical intermediate $\mathbf{III_{1ae}}$ in two resonance forms of 3°-allylic radical ^{a}**III$_{1ae}$** and 1°-allylic radical ^{b}**III$_{1ae}$** (Scheme 3B). In the final step of RS, intermediate **III$_{1ae}$** undergoes 6-*exo-tet* radical cyclization predominately via the less sterically hindered 1°-radical form ^{b}**III$_{1ae}$**, delivering 6-membered cyclic sulfamide **2ae^{a}**. In addition to indicating the involvement of α-Co(III)-aminyl radical intermediate **I$_{1ae}$**, the different outcome of the catalytic reaction by [Co(**P7**)] from [Co(**P5**)] clearly shows the importance of catalytic engineering via ligand design for controlling the course of radical processes. To provide experimental evidence for the formation of γ-Co(III)-alkyl radical intermediate **II** from the intramolecular RA of the initially generated α-Co(III)-aminyl radical intermediate **I**, significant efforts were made toward the direct trapping of the radical intermediate by stable 2,2,6,6,-tetramethyl-1-piperidinyloxy (TEMPO) radical during the catalytic process. More importantly, successful characterization of the TEMPO-trapped product would permit the unequivocal distinction of the two potential catalytic pathways: 5-*exo-trig* cyclization for 5-membered γ-Co(III)-alkyl radical intermediate **II^{a}** (Scheme 2A) and 6-*endo-trig* cyclization for 6-membered γ-Co(III)-alkyl radical intermediate **II^{b}** (Scheme 2B). To this end, the radical bicyclization reaction of *N*-allylsulfamoyl azide **1a** was conducted with the use of catalyst [Co(**P7**)] in the presence of TEMPO (10.0 equiv). Despite adding the large access of TEMPO, [3.1.0]-bicyclic sulfamoyl aziridine **2a** from radical *N*-heterobicyclization was still formed as the major product in 70% yield, indicating the facileness of C–N bond formation via the subsequent RS of γ-Co(III)-alkyl radical intermediate **II** (Scheme 3C). In addition to aziridine **2a**, another compound was isolated from the reaction in 30% yield as a minor product, which was characterized as 6-membered cyclic sulfamide **2a^{a}** containing a TEMPO unit at the quaternary carbon center (see supplemental information for detailed characterizations). The formation of TEMPO-trapped product **2a^{a}** (other than 5-membered cyclic sulfamide **2a^{b}** bearing a TEMPO unit at the primary carbon center) unequivocally supports the preferred operation of the 6-*endo-trig* cyclization pathway of α-Co(III)-aminyl radical intermediate **I$_{1a}$** for the formation of γ-Co(III)-alkyl radical intermediate ^{a}**II$_{1a}$** without involving γ-Co(III)-alkyl radical intermediate ^{b}**II$_{1a}$** (Scheme 3C). As mentioned earlier (Figure 2; entries 32 and 33), when *N*-allylsulfamoyl azides (*Z*)-**1af** and (*Z*)-**1ag** containing (*Z*)-alkene moieties were used as the substrates, the optimal catalyst [Co(**P5**)] could effectively catalyze enantioselective radical *N*-heterobicyclization reactions to afford the corresponding (*Z*)-**2af** and (*Z*)-**2ag**, respectively, with complete preservation of the original (*Z*)-stereochemistry, indicating the kinetic stability of the chiral radical center in the corresponding γ-Co(III)-alkyl radical intermediates **II**. To examine possible ligand effect on the diastereospecificity, reactions of both (*Z*)-**1af** and (*Z*)-**1ag** were performed again under the standard conditions but with the use of [Co(**P7**)] to replace [Co(**P5**)] (Scheme 3D). Remarkably, (*Z*)-**2af** and (*Z*)-**2ag** were produced exclusively in almost quantitative yields (99%) without the observation of the (*E*)-isomers, indicating again the absence of interconversion between the corresponding intermediates (*R*)-**D** and (*S*)-**D** intermediates even with the support of the achiral ligand **P7**. These experimental observations, together with the results from the computational studies, validate the operation of a novel mode of asymmetric induction in radical chemistry that involves 6-*endo-trig* addition of initially generated α-Co(III)-aminyl radical intermediate **I** to terminal olefin unit, giving rise to γ-Co(III)-alkyl radical intermediate **II** bearing kinetically stable chiral radical center on a rigid 6-membered ring before stereospecific annulation via 3-*exo-tet* radical cyclization.

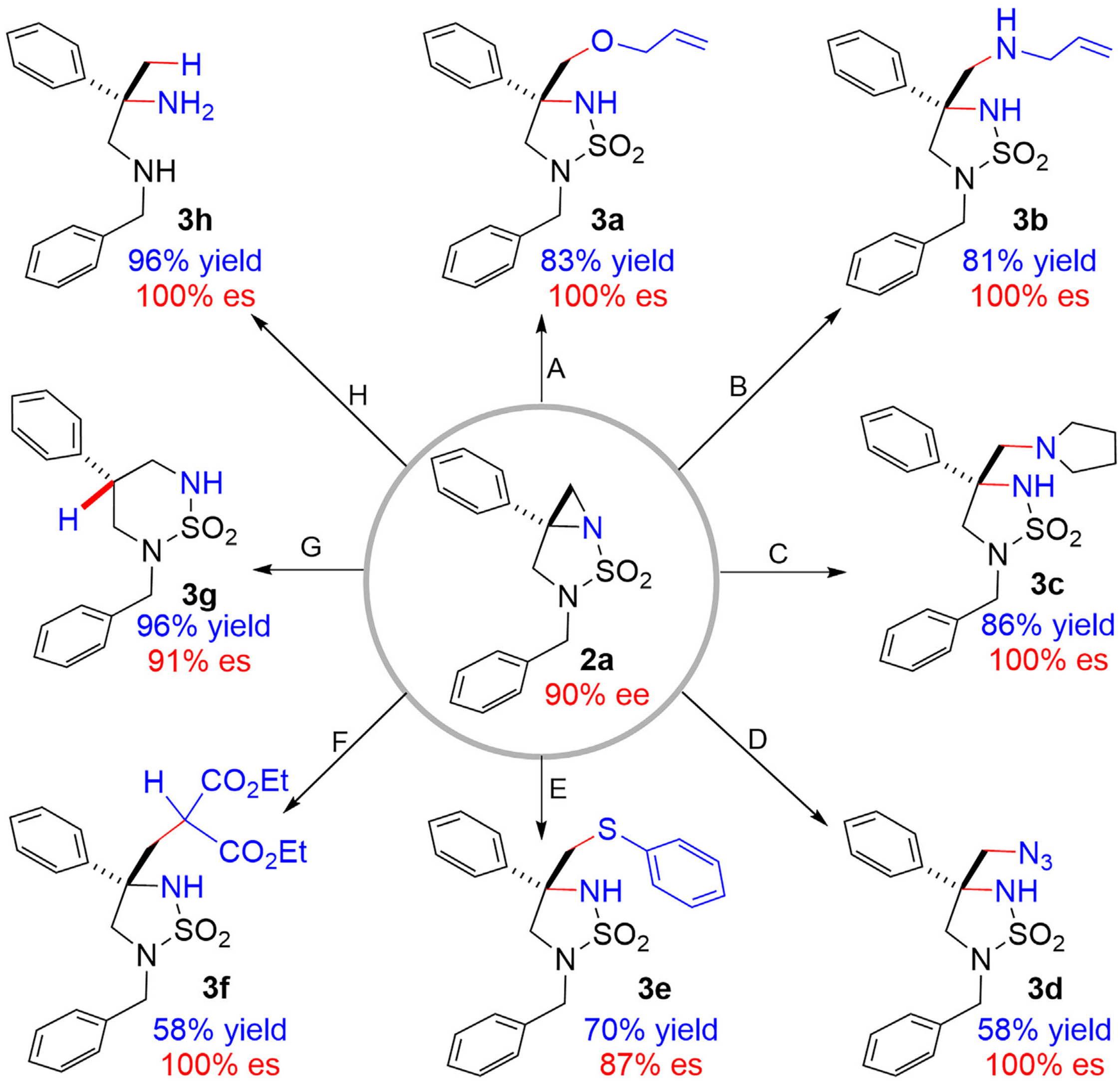
To gain insight into the potential reaction pathway for the catalytic *N*-heterobicyclization of *N*-allylsulfamoyl azides containing terminal alkenes with alkyl substituents and internal alkenes, we performed additional DFT calculation with azides **1y** and (*Z*)-**1ag** as respective representative substrates. For the catalytic reaction involving the alkyl-substituted azide **1y**, the DFT calculations indicate that the corresponding α-Co(III)-aminyl radical intermediate C_{1y} favors 6-*endo-trig* cyclization via the 6-membered T.S. substantially over 5-*exo-trig* cyclization via the 5-membered T.S. ($\Delta\Delta G^{\ddagger}$ = 3.4 kcal/mol) (see Schemes S5 and S6). On the other hand, for the catalytic reaction of the internal alkene-derived azide (*Z*)-**1ag**, it was found that the α-Co(III)-aminyl radical intermediate C_{1ag}, generated from the MRA of (*Z*)-**1ag** by [Co(**P5**)] significantly prefers 5-*exo-trig* cyclization via the 5-membered T.S. over 6-*endo-trig* cyclization via the 6-membered T.S., exhibiting a substantial energy difference ($\Delta\Delta G^{\ddagger}$ = 14.2 kcal/mol) (see Schemes S7 and S8). This finding highlights the dominance of a different RA pathway in the *N*-heterobicyclization of internal alkenes compared with terminal alkenes.

Synthetic application

By taking advantage of the high ring strain in the resulting [3.1.0]-bicyclic sulfamoyl aziridines **2**, the synthetic applications of the Co(II)-catalyzed enantioselective radical *N*-heterobicyclization were showcased with a series of stereospecific ring-opening reactions using enantioenriched aziridine **2a** (90% ee) as a representative example. It was shown that the 3-membered aziridine ring of the *N*-heterobicyclic structure in **2a** could be regioselectively opened at the *exo*-position by disparate nucleophiles, including *O*-, *N*-, *S*-, and *C*-based nucleophiles (Scheme 4). For an example, when reacting with allylic alcohol under the basic condition, **2a** could be regioselectively opened by the *O*-based nucleophile to produce chiral 1,2,3-diamino alcohol derivative **3a** in 83% yield with the retention of the original enantiopurity. As further examples, the regioselective ring-opening of the 3-membered aziridine in **2a** could be effectively carried out with *N*-based nucleophiles such as primary allylic amine, secondary pyrrolidine, and even trimethylsilyl azide under mild conditions, affording the corresponding optically active 1,2,3-triamine derivatives **3b–3d** in good to high yields (58%–86%) with full enantiospecificities (100% es). As another example, thiophenol could function as effective *S*-based nucleophile under the basic condition to react with **2a**, giving the ring-opening product **3e** in 70% yield with 87% es. Furthermore, the ring-opening reaction could also be successfully performed with the use of diethyl malonate as a *C*-based nucleophile in the presence of NaH, providing the corresponding product **3f** in 58% yield with 100% es. Since 5-membered cyclic sulfamides can be readily converted to unprotected 1,2-diamines,[67] the resulting [3.1.0]-bicyclic sulfamoyl aziridines **2** from the Co(II)-catalyzed enantioselective radical *N*-heterobicyclization, in combination with the stereospecific ring-opening process, may serve as useful building blocks for the streamlined preparation of valuable chiral 1,2-diamines bearing various functionalities. To further showcase the synthetic application, it was demonstrated that [3.1.0]-bicyclic sulfamoyl aziridines **2** can also function as chiral building blocks for the stereoselective preparation of optically active 1,3-diamines as exemplified by the selective conversion of **2a** to 1,3-diamine derivative **3g** in 96% yield with 91% es when the aziridine ring was reductively opened at endo-position by H_2 under Pd/C in the presence of diisopropylamine (Scheme 4). Interestingly, when **2a** was treated with lithium aluminium hydride ($LiAlH_{4)}$ in tetrahydrofuran (THF), the aziridine structure of **2a** was selectively opened at the *exo*-position by the hydride and followed by the facile removal of the sulfonyl group, directly producing unprotected 1,2-diamine **3h** in 96% yield with 100% es, which could be further converted to the corresponding imidazolidinone **3i** in 74% yield without the erosion of the original enantiopurity upon reacting with carbonyldiimidazole (see supplemental information for details).

Conclusions

In summary, we have successfully developed the first catalytic system for the enantioselective radical *N*-heterobicyclization of *N*-allylsulfamoyl azides via Co(II)-based MRC.



Scheme 4. Stereospecific ring-opening reactions of optically active [3.1.0]-bicyclic sulfamoyl aziridines

(A) 2-propen-1-ol (10.0 equiv); sodium hydride (10.0 equiv); THF/dimethylsulfoxide (DMSO) (1/1); 0°C to room temperature (RT); 12 h.
(B) 2-propen-1-amine (5.0 equiv); THF/DMSO (1/1); 40°C; 12 h.
(C) Pyrrolidine (5.0 equiv); THF/DMSO (1/1); 40°C; 12 h.
(D) Trimethylsilyl azide (2.0 equiv); tetrabutylammonium fluoride (2.0 equiv); THF; RT; 12 h.
(E) Thiophenol (5.0 equiv); sodium hydride (5.0 equiv); THF/DMSO (1/1); 0°C to RT; 12 h.
(F) Diethyl malonate (4.0 equiv); sodium hydride (2.0 equiv); THF/DMSO (1/1); 40°C; 12 h.
(G) Pd/C (0.1 equiv); H_2; diisopropylamine (5.0 equiv); ethanol (EtOH); RT; 3 h.
(H) $LiAlH_4$ (5.0 equiv); THF; 90°C; 12 h; ee measured with its further transformation product **3i** (see supplemental information).

With the D_2-symmetric chiral bridged amidoporphyrin 3,5-Di^{t}Bu-Hu(C_6)Phyrin as the optimal supporting ligand, the Co(II)-based metalloradical system can homolytically activate allylic sulfamoyl azides with varied electronic and steric properties for asymmetric radical *N*-heterobicyclization under mild conditions without the need of oxidants or any additives, allowing for the stereoselective construction of chiral [3.1.0]-bicyclic sulfamoyl aziridines in excellent yields with high diastereoselectivities and enantioselectivities. Fundamentally, we have unveiled a new mode of asymmetric induction in radical chemistry that involves 6-*endo-trig* addition of initially formed α-Co(III)-aminyl radical to a terminal olefin unit. Through the combination of comprehensive experimental and computational studies, we have demonstrated that the γ-Co(III)-alkyl radical intermediate formed from the RA bears kinetically stable chiral radical center on a rigid 6-membered ring and can readily undergo stereospecific annulation reaction via 3-*exo-tet* radical cyclization without racemization. We have shown that the linchpin to control the challenging enantioface selectivity in the RA is the fine-tuning of the ligand environment of new-generation D_2-symmetric chiral bridged amidoporphyrin HuPhyrins through the judicious variation of the alkyl bridge length to dictate both the reactivity and selectivity of Co(II)-based MRC. As showcased by a number of enantiospecific transformations of the resulting enantioenriched [3.1.0]-bicyclic sulfamoyl aziridines for the preparation of valuable chiral 1,2-diamine and 1,3-diamine derivatives, we believe that this Co(II)-based metalloradical system for asymmetric radical *N*-heterobicyclization process may find useful synthetic applications.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

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

Materials availability

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

Data and code availability

The crystal structure data of compounds (*R*)-**2i**, (*R*)-**2j**, and (*S*,*R*)-**2af** have been deposited in the Cambridge Structural Database under reference numbers CCDC: 2211360, 2106738, and 2211361, respectively.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2023.09.010.

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AUTHOR CONTRIBUTIONS

H.X. conducted the experiments and the DFT calculations. D.-S.W. assisted the DFT calculations. Z.Z., A.D., and D.-S.W. assisted the experiments. X.P.Z. conceived the work and directed the project. H.X. and X.P.Z. designed the experiments. H.X., D.-S.W., and X.P.Z. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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