

Asymmetric Induction and Enantiodivergence in Catalytic Radical C–H Amination via Enantiodifferentiative H-Atom Abstraction and Stereoretentive Radical Substitution

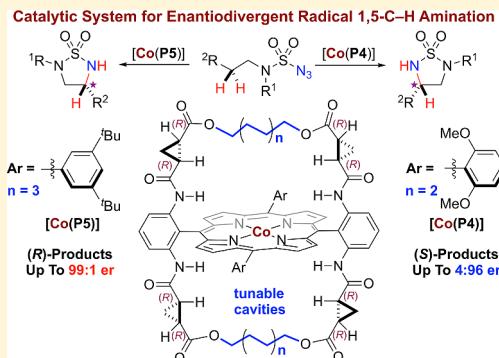
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Supporting Information

ABSTRACT: Control of enantioselectivity remains a major challenge in radical chemistry. The emergence of metalloradical catalysis (MRC) offers a conceptually new strategy for addressing this and other outstanding issues. Through the employment of D_2 -symmetric chiral amidoporphyrins as the supporting ligands, Co(II)-based MRC has enabled the development of new catalytic systems for asymmetric radical transformations with a unique profile of reactivity and selectivity. With the support of new-generation HuPhyrin chiral ligands whose cavity environment can be fine-tuned, the Co-centered d-radicals enable to address challenging issues that require exquisite control of fundamental radical processes. As showcased with asymmetric 1,5-C–H amination of sulfamoyl azides, the enantiocontrol of which has proven difficult, the judicious use of HuPhyrin ligand by tuning the bridge length and other remote nonchiral elements allows for controlling both the degree and sense of asymmetric induction in a systematic manner. This effort leads to successful development of new Co(II)-based catalytic systems that are highly effective for enantiodivergent radical 1,5-C–H amination, producing both enantiomers of the strained five-membered cyclic sulfamides with excellent enantioselectivities. Detailed deuterium-labeling studies, together with DFT computation, have revealed an unprecedented mode of asymmetric induction that consists of enantiodifferentiative H-atom abstraction and stereoretentive radical substitution.



1. INTRODUCTION

Aminyl radicals have been increasingly explored as synthetic intermediates for the formation of C–N bonds.¹ Among important applications, the N-centered radicals have been commonly employed in intramolecular fashion for construction of N-heterocyclic structures, primarily via radical addition (RA) to unsaturated π -bonds in combination with H-atom abstraction (HAA) (Scheme 1a).² Although mechanistically appealing, the alternative heterocyclization that is based on the association of H-atom abstraction (HAA) and radical substitution (RS) has been seldom documented (Scheme 1b). While abstraction of C–H bonds by aminyl radicals via intramolecular H-atom abstraction is typically facile, the subsequent C–N bond formation via homolytic radical substitution at the nitrogen center by the resulting alkyl radicals has not been well demonstrated and is presumably difficult.³ The well-known Hofmann–Löffler–Freytag (HLF) reaction obviates this inherent challenge to achieve C–N bond formation by switching the substitution step from radical to nucleophilic pathway.⁴ One potential direct solution to this fundamental problem would be the utilization of α -metalloaminyl radicals $R(L_nM)N\cdot$ instead of free aminyl radicals $RR'N\cdot$ (Scheme 1c).⁵ In view of the lower strength and higher polarity of M–N than C–N bonds, the otherwise difficult

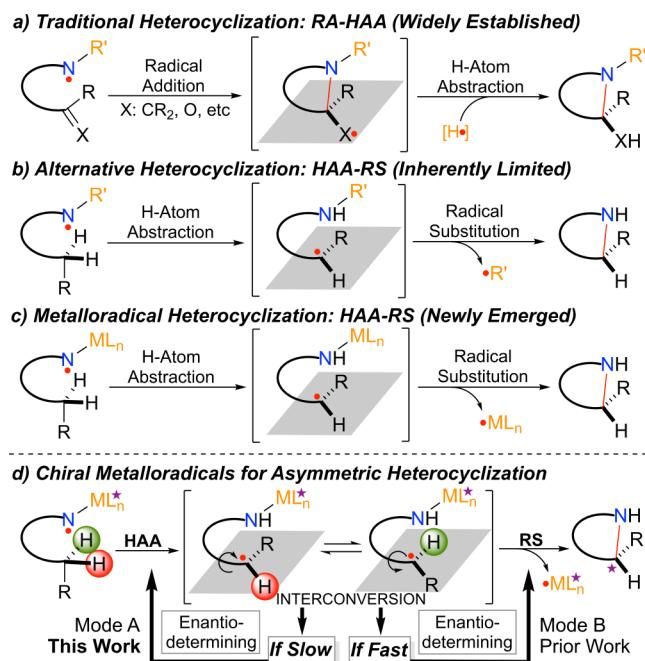
radical substitution would become both thermodynamically possible and kinetically feasible, especially with the generation of stable metalloradicals ($L_nM\cdot$). Furthermore, this metalloradical-based approach for radical heterocyclization has the possibility to be turned over catalytically with the promise of controlling enantioselectivity as illustrated with two potential modes of asymmetric induction (Scheme 1d).

Homolytic radical reactions have vast synthetic potentials and could impact the practice of organic synthesis, which has been dominated by heterolytic ionic reactions. Despite recent advancements, the enduring issue of enantioselectivity remains largely unaddressed for most radical reactions.⁶ Among recent strategies,⁷ metalloradical catalysis (MRC) offers a conceptually different approach for achieving stereoselective radical reactions by exploiting metal-centered radicals for catalytic generation of metal-stabilized organic radicals that undergo subsequent radical transformations under the catalyst control.^{8,9} To this end, Co(II) complexes of porphyrins, as stable 15e metalloradicals, have shown the unusual capability of activating organic azides to generate the fundamentally new α -Co(III)-aminyl radicals.¹⁰ With the employment of D_2 -

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Scheme 1. Heterocyclization Pathways of Aminyl Radicals and Potential Modes of Asymmetric Induction

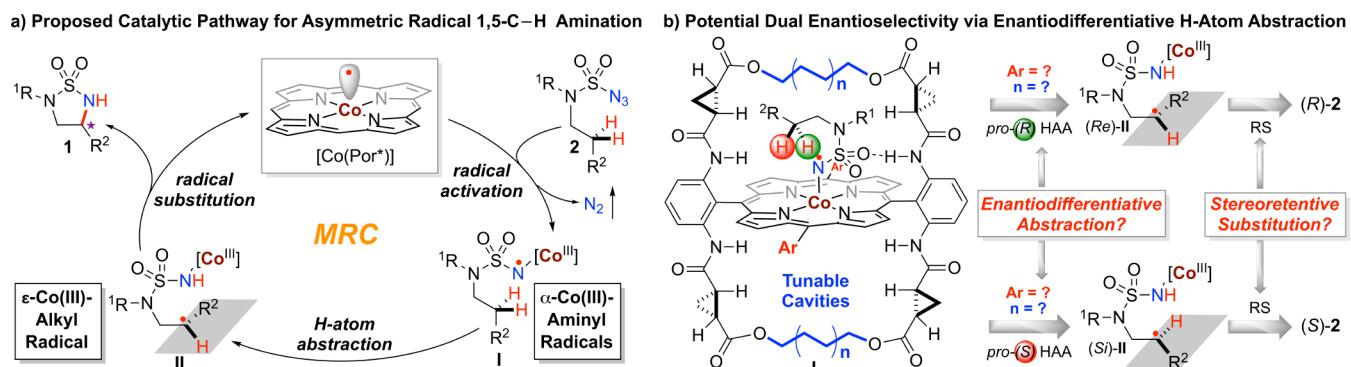


symmetric chiral amidoporphyrins as the supporting ligands, the α -metalloaminyl radicals can undergo radical addition and H-atom abstraction as well as radical substitution, leading to the development of new catalytic processes for enantioselective radical transformations.¹¹ Among them, we recently demonstrated the aforementioned radical heterocyclization strategy for the construction of strained five-membered cyclic sulfamides from sulfamoyl azides, which was difficult by concerned ionic pathway.¹² To develop an asymmetric version of the catalytic process (Scheme 2a), we were attracted by the possibility of controlling enantioselectivity via both modes of asymmetric induction (Scheme 1d). In the course of pursuing the common Mode B for asymmetric induction with Co(II) complexes of existing open D_2 -symmetric chiral amidoporphyrins,^{11d,13} the recent introduction of new-generation D_2 -symmetric chiral amidoporphyrins HuPhyrin,¹⁴ which contain bridges across two chiral amide units on both sides of the porphyrin plane where the metal-centered d-radical is encapsulated inside a chiral cavity, prompted us to explore the rare Mode A for asymmetric induction. Under the support

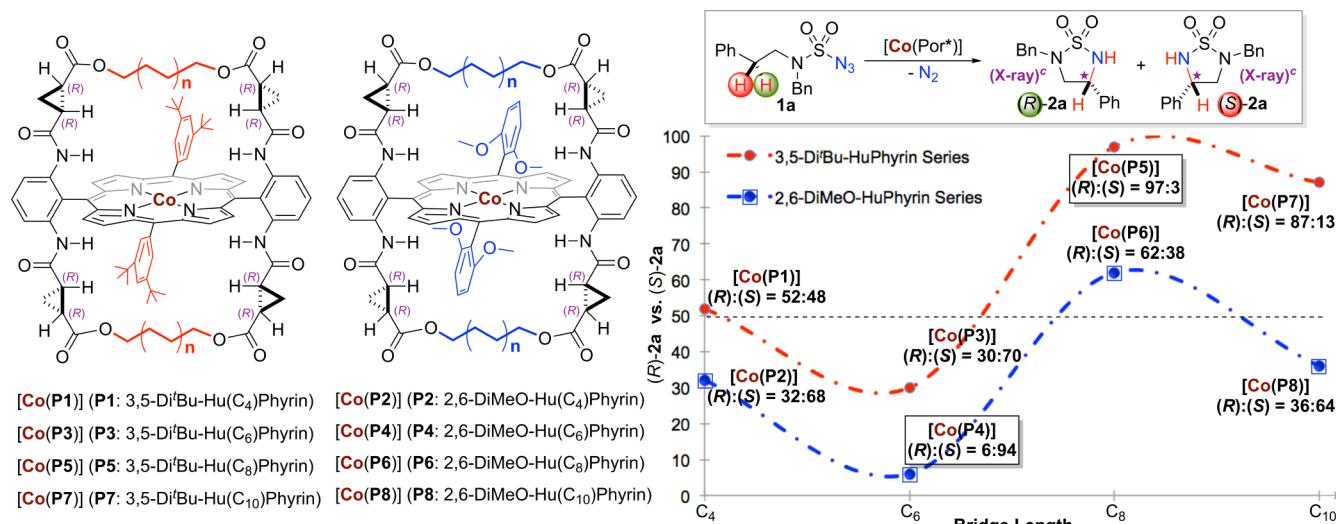
of HuPhyrin ligand with a proper cavity environment, we imagined that the corresponding α -Co(III)-aminyl radical I could be governed for enantiodifferentiative H-atom abstraction (HAA) of either pro-(R) or pro-(S) hydrogen (Scheme 2b).¹⁵ If the newly created facial chirality in the resulting ϵ -Co(III)-alkyl radical II could be conformationally stabilized by the geometric constraints inside the confined space,¹⁶ the subsequent intramolecular radical substitution (RS) could be enabled stereoretentive, forming five-membered cyclic sulfamides with the enantioselectivity that is predetermined in the HAA step (Scheme 2b). Catalyst engineering by fine-tuning the length of the distal bridge in combination with the remote meso-aryl substituents might allow achieving enantiodivergence for the catalytic radical process,^{17,18} which would be desirable considering that both enantiomers of a chiral catalyst are not always accessible from available chiral sources. If this type of unprecedented radical amination could be realized, it would be fundamentally appealing and practically useful as the resulting five-membered cyclic sulfamides and related vicinal diamines in both (R)- and (S)-configurations are common structural motifs in biologically important molecules (see Figure S1 in the Supporting Information).

Intramolecular C–H amination via metal-catalyzed nitrene transfer represents a general approach for stereoselective construction of chiral N-heterocycles through direct functionalization of ubiquitous C–H bonds in organic molecules. Despite recent progresses,^{19,20} the development of chiral catalysts for asymmetric intramolecular amination is still limited. In particular, catalytic asymmetric intramolecular 1,5-C–H amination to synthesize optically active five-membered cyclic sulfamides remains to be developed. As the first demonstration of the aforementioned Mode A for asymmetric induction, we herein wish to report the development of Co(II)-based metalloradical system with the support of the new type of bridged D_2 -symmetric chiral amidoporphyrins HuPhyrin for asymmetric intramolecular 1,5-C–H amination of sulfamoyl azides. Using HuPhyrin with varied bridge length and different substituents, both the degree and sense of asymmetric induction in the Co(II)-catalyzed amination can be effectively controlled in a systematic way. Two optimal catalysts, which differ only by the remote elements, have emerged from this study that can catalyze the efficient formation of the strained five-membered cyclic sulfamides as the opposite enantiomers, respectively, with high enantioselectivity. This enantiodivergent process is applicable to a broad scope of substrates. Our mechanistic studies support an

Scheme 2. Toward Enantiodivergence for Intramolecular Radical 1,5-C–H Amination by Co(II) Complexes of Bridged D_2 -Symmetric Chiral Amidoporphyrins



Scheme 3. Systematic Control of Degree and Sense of Asymmetric Induction in Intramolecular Radical 1,5-C–H Amination of Sulfamoyl Azide by [Co(HuPhyrin)]^{a,b,c,d}



^aReactions were performed on a 0.10 mmol scale of sulfamoyl azide **1a** using 2 mol % of [Co(HuPhyrin)] in 1.0 mL of methyl *tert*-butyl ether (MTBE) at 40 °C; **1a** = 0.10 M. ^bYields in the Supporting Information. ^cAbsolute configuration determined by X-ray crystal structural analysis.

^dEnantiomeric ratios (er) determined by chiral HPLC analysis.

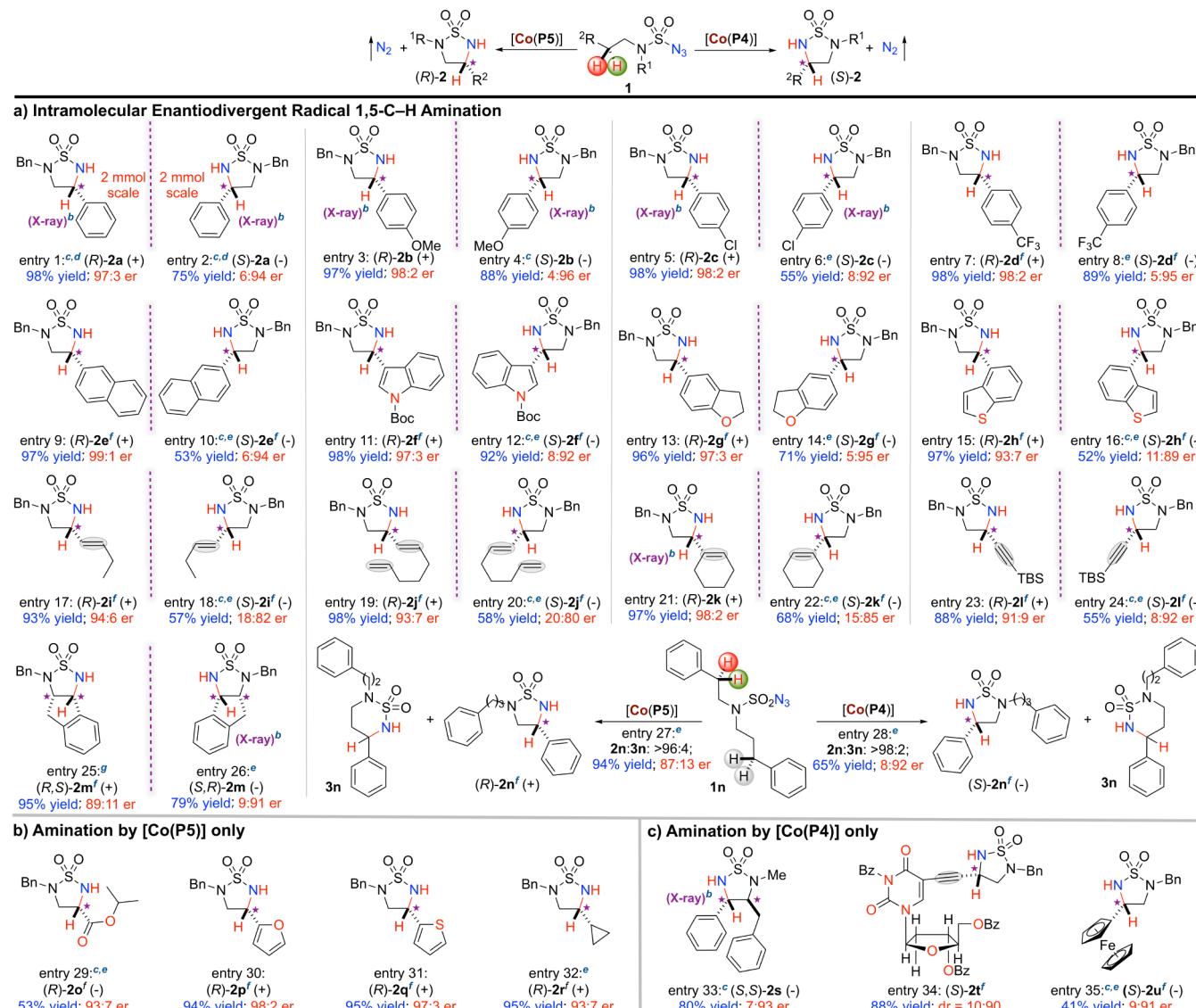
unprecedented mode of asymmetric induction that consists of enantiodifferentiative HAA and stereoretentive RS.

2. RESULTS AND DISCUSSION

At the outset of this project, sulfamoyl azide **1a** containing benzylic C–H bonds was selected as a test substrate for Co(II)-catalyzed radical 1,5-C–H amination. To explore the ligand effect on asymmetric induction during the Co(II)-catalyzed radical amination, we employed two series of HuPhyrin ligands that are based on 3,5-di-*t*-butylphenyl and 2,6-dimethoxyphenyl groups as 5,15-aryl substituents, respectively (Scheme 3). Both series of HuPhyrin contain the identical chiral amide element and the same type of alkyl bridge; they differ only by the bridge length varying from 4 to 6 to 8 to 10 methylene units. As illustrated in Scheme 3, the length of the distal alkyl bridge in HuPhyrin could significantly affect the asymmetric induction of the Co(II)-catalyzed C–H amination of azide **1a**. Variation of the bridge length by two methylene units each time resulted in systematic alteration in enantioselectivity and even led to the switch in the sense of asymmetric induction for the formation of five-membered cyclic sulfamide **2a** (Scheme 3). For [Co(3,5-Di*t*Bu-HuPhyrin)] catalyst series, C₄-bridged [Co(P1)] slightly favored the formation of (R)-**2a** (52:48 er) while C₆-bridged [Co(P3)] produced (S)-**2a** as the major enantiomer (30:70 er). When the alkyl bridge was further extended to C₈-linker in [Co(P5)], the sense of asymmetric induction switched back again, forming (R)-**2a** in high enantioselectivity (97:3 er). The effect continued for C₁₀-bridged [Co(P7)], which still produced (R)-**2a** as the major enantiomer but with decreased enantioselectivity (87:13 er). Interestingly, a parallel trend in asymmetric induction was also observed for the reaction by [Co(2,6-DiMeO-HuPhyrin)] catalyst series, generating **2a** with (R):(S) enantiomer ratio varying from 32:68 by C₄-bridged [Co(P2)] to 6:94 by C₆-bridged [Co(P4)] to 62:38 by C₈-bridged [Co(P6)] to 36:64 by C₁₀-bridged [Co(P8)]. Consequently, the five-membered cyclic chiral sulfamide could be enantiodivergently constructed through C–H amination by

the use of C₆-bridged [Co(P4)] and C₈-bridged [Co(P5)] as the catalysts, producing highly enantioenriched (S)-**2a** and (R)-**2a**, respectively (Scheme 3). Considering that the only differences between [Co(P4)] and [Co(P5)] are the distal alkyl bridges and the remote nonchiral substituents, it is remarkable that such enantiodivergence could be realized under the same catalytic conditions.

The enantiodivergent radical 1,5-C–H amination exerted by the pair of metalloradical catalysts [Co(P4)] and [Co(P5)] was found general and could be broadly applicable to various sulfamoyl azides with different types of C–H bonds (Table 1a). For the catalytic amination reactions of azide **1a** by [Co(P4)] and [Co(P5)], they could be scaled up 20 times (from 0.1 to 2.0 mmol) under the standard conditions, producing (S)-**2a** and (R)-**2a**, respectively, in similarly high yields with the same excellent enantioselectivities (entries 1 and 2). Other benzylic C–H bonds with varied electronic properties could also be aminated in high yields with excellent enantioselectivities as shown for formation of both (R)- and (S)-cyclic sulfamides **2b**–**2d** (entries 3–8). In addition, highly enantiodivergent stereocontrol was observed for amination of benzylic C–H bonds in both polycyclic and heteroaromatic systems, as demonstrated for the productive formation of naphthalene-based **2e** (entries 9 and 10), indole-based **2f** (entries 11 and 12), dihydrobenzofuran-based **2g** (entries 13 and 14), and benzothiophen-based **2h** (entries 15 and 16). Furthermore, this enantiodivergent system exhibited excellent chemoselectivity toward radical amination of allylic C–H bonds to afford allylic 1,2-diamine derivatives without affecting the C=C double bonds, including monoene (**2i**), diene (**2j**), and cyclic ene (**2k**) (entries 17–22). Similarly, propargylic C–H bonds could be chemoselectively aminated as exemplified by enantiodivergent formation of propargylic 1,2-diamine derivative **2l** without the involvement of the electron-rich C≡C bond (entries 23 and 24).²¹ Additionally, the Co(II)-based enantiodivergent system could be successfully applied for the desymmetrization of 2-indane-derived sulfamoyl azide to form the cis-fused tricyclic sulfamide **2m** with effective control of the

Table 1. Substrate Scope of Intramolecular Radical 1,5-C–H Amination of Sulfamoyl Azides via Co(II)-Based MRC^a

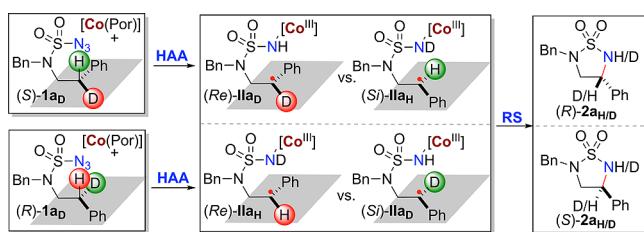
^aReactions were performed on a 0.10 mmol scale of sulfamoyl azide 1 using 2 mol % [Co(Por*)] in 1.0 mL of methyl *tert*-butyl ether (MTBE) at room temperature; enantiomeric ratios (er) determined by chiral HPLC analysis. ^bAbsolute configuration determined by X-ray crystal structural analysis. ^cAt 40 °C. ^dPerformed at 2.0 mmol scale with 2 mol % of [Co(Por*)]. ^e5 mol % [Co(Por*)]. ^fAbsolute configuration assigned by analogy. ^gWhen N-Bn was replaced by N-iPr: 61% yield; 94:6 er.

two newly generated stereogenic centers (entries 25 and 26). Moreover, the cavity environment of [Co(P4)] and [Co(P5)] enabled the enantiodivergent system with uncommon regioselectivity. This was nicely illustrated by the reactions of sulfamoyl azide **1n** bearing sterically and electronically similar benzylic C–H bonds where both 1,5- and 1,6-C–H amination could potentially occur (entries 27 and 28).^{11d,12} Remarkably, five-membered cyclic sulfamides **2n** were regioselectively constructed in high enantiodivergent selectivities over the less-strained six-membered cyclic sulfamides **3n**.^{11d,12}

A set of mechanistic experiments were performed to obtain direct evidence for the proposed stepwise radical pathway of the Co(II)-catalyzed 1,5-C–H amination.^{10a–c} As detailed in the Supporting Information, the corresponding α -Co(III)-aminyl radical **I** from the reaction of azide **1a** could be directly detected by EPR and HRMS (Figure S6 and S7). In the presence of excess TEMPO (10 equiv), the resulting ε -

Co(III)-alkyl radical **II** after 1,5-H-atom abstraction could be successfully trapped, generating a TEMPO-substituted product along with the amination product **2a** (see the Supporting Information). To determine the mode of asymmetric induction in the enantiodivergent system by [Co(P4)] and [Co(P5)], isotopomeric sulfamoyl azides in optically pure form (*S*)-**1a_D** and (*R*)-**1a_D** were prepared as substrates to study kinetic isotope effects (KIE) on C–H radical amination (Table 2). With the achiral nonbridged catalyst [Co(P9)] (**P9** = 3,5-Di^tBu-IbuPhyrin), the intramolecular KIE was measured to have the same high value of 23.0 for reactions of both azides (*S*)-**1a_D** and (*R*)-**1a_D** (entries 1 and 4), which suggests significant tunneling that might be related to the high-strained transition state of the HAA process. When chiral catalysts are employed, alteration of this intrinsic KIE will be expected because of chirality match and mismatch between the catalyst and substrate. Accordingly, the use of chiral catalyst [Co(P4)]

Table 2. KIE Studies on Catalytic C–H Amination of Enantiopure Isotopomeric Azides via Co(II)-Based MRC^{a,b,c}



entry	azide	catalyst	KIE ^b	Re:Si of IIa ^c	ee% ^{cal,d}	ee% ^{exp,e}
1	(S)-1a _D	[Co(P9)]	23.0	96:4	92 (R)	4 (R)
2 ^f	(S)-1a _D	[Co(P4)]	2.0	67:33	34 (R)	−4 (S)
3	(S)-1a _D	[Co(P5)]	96.0	99:1	98 (R)	94 (R)
4	(R)-1a _D	[Co(P9)]	23.0	4:96	−92 (S)	−4 (S)
5 ^f	(R)-1a _D	[Co(P4)]	61.0	2:98	−96 (S)	−94 (S)
6	(R)-1a _D	[Co(P5)]	0.8	57:43	14 (R)	32 (R)

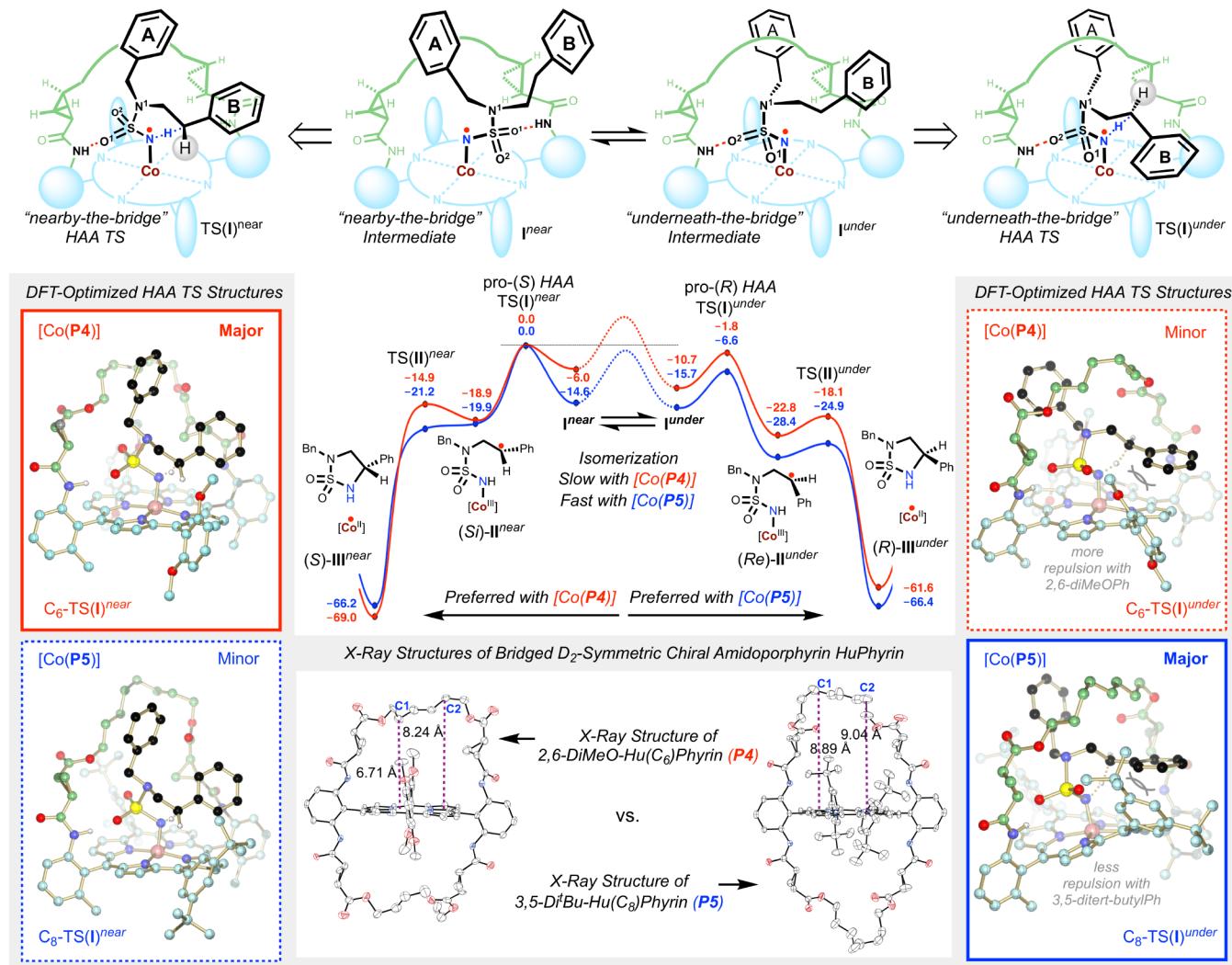
^aReactions were performed on a 0.10 mmol scale of sulfamoyl azide (R)-1a_D or (S)-1a_D using 2 mol % of [Co(Por)] in 1.0 mL of MTBE at 40 °C; yields in the Supporting Information. ^bRatio of H:D determined by ¹H NMR spectroscopy. ^cCalculated based on the ratio of H:D. ^dee of 2a calculated on the basis of stereoretentive RS. ^eee of 2a determined by chiral HPLC analysis, which offered no separation of (R)-2a_H from (R)-2a_D and (S)-2a_H from (S)-2a_D. ^f5 mol % [Co(P4)].

resulted in a lower KIE value of 2.0 for (S)-1a_D (entry 2) while a higher KIE value of 61.0 for (R)-1a_D (entry 5) was obtained, indicating enantiodifferentiative abstraction of pro-(S) H-atom by [Co(P4)]. On the other hand, chiral catalyst [Co(P5)] raised the KIE to a value of 96.0 for (S)-1a_D (entry 3) but lowered it to a value of 0.8 for (R)-1a_D (entry 6), suggesting that [Co(P5)] abstracted pro-(R) H-atom enantiodifferentiatively. Based on the measured KIE values, the ratios of the initially established two chiral faces (Re)-IIa to (Si)-IIa could be deduced. And in turn, it permits the calculation of predicted enantiomeric excess (ee) of the amination products 2a based on the assumption that there is no racemization of the face chirality during the subsequent RS step. The fact that the measured ee of product 2a by HPLC for the amination reaction of (S)-1a_D by [Co(P5)] agreed near completely with the predicted value revealed stereoretentive RS during the catalytic process (entry 3). Likewise, the RS step for catalytic amination reaction of (R)-1a_D by [Co(P4)] was also concluded to be stereoretentive (entry 5). In contrast to [Co(P4)] and [Co(P5)], however, the data suggested that the RS in the catalytic process by the nonbridged catalyst [Co(P9)] is nonstereoretentive (entries 1 and 4). Presumably due to less geometric constraints exerted by the open catalyst [Co(P9)], the highly enantioenriched facial chirality established in the first HAA step from both reactions of (S)-1a_D (entry 1) and (R)-1a_D (entry 4) was near completely racemized through low-barrier rotation of the α-C–C bond in the corresponding radical intermediate IIa. Clearly, the cavity environment in [Co(P4)] and [Co(P5)] created by bridging is primarily contributed to the realization of this unprecedented mode of asymmetric induction in the catalytic radical process by combining highly enantiodifferentiative HAA with completely retentive RS (Scheme 1d, Mode A).

To shed light on the origin of this new mode of asymmetric induction, the transition states (TS) of the HAA step in the

reaction of azide 1a by C₆-bridged [Co(P4)] and C₈-bridged [Co(P5)] catalysts were calculated with density functional theory (DFT) at the ω-B97XD/Def2TZVPP//M06L/Def2SVP_{benzene(SMD)} level (see the Supporting Information for details). The DFT calculations revealed two possible low-energy conformers I_{under} and I_{near} for α-Co(III)-aminyl radical intermediate I, where phenyl ring A is located “underneath-the-bridge” and “nearby-the-bridge”, respectively (Scheme 4, top panel). Accordingly, two major TS were identified for HAA: the most stable underneath-the-bridge TS(I)_{under} and the next stable nearby-the-bridge TS(I)_{near}, enabling pro-(R) HAA to generate ε-Co(III)-alkyl radical intermediate (Re)-II_{under} and pro-(S) HAA to form ε-Co(III)-alkyl radical intermediate (Si)-II_{near}, respectively (Scheme 4). In both TS, the chiral cyclopropane unit on the left serves as a primary source for asymmetric induction by forcing phenyl ring B into the front right quadrant. Consistent with the experimental observations, the bridge lengths (C₆ vs C₈) as well as the identity of the nonchiral substituents (2,6-DiMeO vs 3,5-Di^tBu) appear to be pivotal to reach specific TS. The larger cavity created by the C₈-bridge in [Co(P5)] significantly favors C₈-TS(I)_{under} (−6.6 kcal/mol below C₈-TS(I)_{near}), where the pro-(R) benzylic hydrogen is oriented in closer proximity to the nitrogen radical for HAA so as to avoid the steric interaction of phenyl ring B with the distal 3,5-Di^tBu groups. In the smaller [Co(P4)] system, C₆-TS(I)_{under} is also lower in energy than C₆-TS(I)_{near}, albeit to a lesser degree (−1.8 kcal/mol). Considering that the C₆-bridge is too small to allow isomerization from C₆-I_{near} to C₆-I_{under}, we propose that access to C₆-TS(I)_{under} is kinetically difficult. This is well illustrated by the DFT-optimized ball-and-stick models of C₆-TS(I) and C₈-TS(I), which are consistent with the structural details of P4 and P5 provided by single-crystal X-ray diffraction analysis (Scheme 4). Consequently, [Co(P4)] is governed to adopt C₆-TS(I)_{near}, in which the pro-(S) benzylic hydrogen is better positioned to approach the nitrogen radical for HAA in order to prevent steric clash between the protruding phenyl ring B and the proximal 2,6-DiMeO moieties. Collectively, the DFT studies allowed us to establish agreeable stereochemical models where productive HAA can be achieved enantiodifferentiatively through TS(I)_{near} or TS(I)_{under}, depending on the cavity size underneath the distal bridge, which turns on and off the isomerization from intermediate I_{near} to I_{under}, eventually leading to the opposite asymmetric induction. The low barriers associated with radical substitution (TS(II)_{near} and TS(II)_{under}) together with the hindered racemization of the chiral face in ε-Co(III)-alkyl radical intermediate II are consistent with a stereoretentive RS step.

These stereochemical models were further substantiated by additional experiments that employed substrates with unique steric or electronic properties to probe difference in reactivity and stereoselectivity (Table 1, entries 29–35). First, when azides 1o–1q bearing heteroatoms in proximity to the C–H site were used as the substrates, the catalytic reactions by [Co(P4)] were inefficient (<10% yields even at 40 °C) (see the Supporting Information) while [Co(P5)] could catalyze the high-yielding formation of the desired amination products 2o–2q with high (R)-enantioselectivities (Table 1b, entries 29–31). The negative outcomes of these catalytic reactions by [Co(P4)] are attributed to the high barrier to reach the dominated C₆-TS(I)_{near} owing to the lone-pair repulsion between heteroatom in the substrates and the oxygen of 2,6-DiMeO groups in the catalyst. Such unfavorable repulsive

Scheme 4. DFT-Optimized Stereochemical Models of Enantiodifferentiative H-Atom Abstraction by $[\text{Co}(\text{P}4)]$ and $[\text{Co}(\text{P}5)]$ ^a

^aSee the Supporting Information for movies of the major pathways leading to the enantiodifferentiative HAA and stereoreactive RS by $[\text{Co}(\text{P}4)]$ and $[\text{Co}(\text{P}5)]$.

interactions are absent with the 3,5-Di^tBu groups in $[\text{Co}(\text{P}5)]$ through $\text{C}_8\text{-TS}(\text{I})^{\text{under}}$. The productive formation of (R)-**2o** (entry 29) is particularly noteworthy both fundamentally and practically in view of the difficulty associated with amination of the electron-deficient α -C–H bonds of ester by C–H insertion via electrophilic metallocenitrenes as well as the importance of the resulting α , β -diamino acid ester as a recurring core unit in a variety of bioactive compounds.²² As a probe for steric effect, azide **1r** carrying a less sterically hindered cyclopropyl moiety adjacent to the C–H site was found to be efficiently aminated by $[\text{Co}(\text{P}5)]$ to afford the desired **2r** with high (R)-enantioselectivity (entry 32) whereas the use of $[\text{Co}(\text{P}4)]$ led to the formation of **2r** with moderate (R)-enantioselectivity (58:42 er) (see the Supporting Information). Considering the similar size of the two *N*-substituents (cyclopropylethyl vs phenylmethyl), such low and anomalous (R)-enantioselectivity by $[\text{Co}(\text{P}4)]$ agrees well with the general models because of the decreased preference for the cyclopropyl moiety to stay in the front right quadrant to react in the dominated $\text{C}_6\text{-TS}(\text{I})^{\text{near}}$. The high-yielding reaction of substrate **1r** (Table 1, entry 32) indicated that the rate of homolytic substitution is faster than the rate of ring-opening of the cyclopropylcarbinyl radical. On

the other hand, azides **1s**–**1u** bearing bulky groups could be productively aminated by $[\text{Co}(\text{P}4)]$ to produce the desired **2s**–**2u** with high (S)-enantiocontrol (Table 1c, entries 33–35), indicating that the majority of steric bulkiness in these substrates was effectively directed outside the catalyst cavity in the corresponding $\text{C}_6\text{-TS}(\text{I})^{\text{near}}$. In addition to demonstrating the suitability for large substrates, the productive formation of cyclic sulfamides **2t** containing densely functionalized deoxyuridine highlights the remarkable degree of functional group tolerance by the catalytic system (entry 34). It is also notable that $[\text{Co}(\text{P}4)]$ could effectively desymmetrize the two benzyl groups in azide **1s**, leading to *trans*-(*S,S*)-**2s** with effective control of the two newly generated stereogenic centers (entry 33). However, when $[\text{Co}(\text{P}5)]$ was used as the catalyst, the catalytic reactions of azides **1s**–**1u** afforded the amination products **2s**–**2u** with moderate (R)-enantioselectivity (~58:42 er) (see the Supporting Information). As well, these results are considered to be consistent with the general models in view of the decreased preference for $\text{C}_8\text{-TS}(\text{I})^{\text{under}}$ over $\text{C}_8\text{-TS}(\text{I})^{\text{near}}$ as a result of the large size associated with these substrates. Furthermore, the observed systematic variation in enantiodi-

vergence described in **Scheme 3** appears to be well consistent with the stereochemical models.

3. CONCLUSIONS

In summary, we have demonstrated an unprecedented mode of asymmetric induction in radical process that is based on sequential combination of enantiodifferentiative H-atom abstraction (HAA) and stereoretentive radical substitution (RS). Under Co(II)-based metalloradical catalysis (MRC), this new mode of asymmetric induction has been put in practice for successful development of the first asymmetric system for stereoselective synthesis of the strained five-membered cyclic sulfamides via radical 1,5-C–H amination of sulfamoyl azides. With the support of bridged HuPhyrin ligands, whose chiral cavity can be fine-tuned by varying the combination of the distal alkyl bridges and the remote nonchiral substituents, Co(II)-based metalloradical system has been shown to have an unusual capability of controlling both the degree and sense of asymmetric induction in the catalytic radical C–H amination in a systematic manner. A pair of similar metalloradical catalysts $[\text{Co}(\text{P}4)]$ and $[\text{Co}(\text{P}5)]$, which differ only by the length of the distal alkyl bridges and the position of the remote nonchiral substituents, have been identified as effective catalysts for the enantiodivergent radical C–H amination with high enantioselectivity under the same mild conditions. The enantiodivergent system is applicable to a broad scope of substrates with different types of $\text{C}(\text{sp}^3)$ –H bonds and exhibits a remarkable profile of reactivity and selectivity, providing access to both enantiomers of useful five-membered cyclic sulfamides in a highly enantioenriched form. In addition to shedding light on the origin of the asymmetric induction in the current catalytic system, the stereochemical models, established on the basis of the combined experimental and computational studies, may have far-reaching implications for how to design catalysts for enantioselective radical reactions. This study paves the way for further exploration of unrecognized potential of radical reactions in stereoselective organic synthesis, including development of catalytic radical processes for enantiodivergent synthesis of chiral molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.9b05850](https://doi.org/10.1021/jacs.9b05850).

Experimental details, supplementary figures, and spectroscopic data ([PDF](#))

Coordinates for DFT-calculated structures ([XYZ](#))

Movie for major C–H amination pathway by $[\text{Co}(\text{P}4)]$ ([MP4](#))

Movie for major C–H amination pathway by $[\text{Co}(\text{P}5)]$ ([MP4](#))

Crystallography data for *(R)*-**2a**, *(S)*-**2a**, *(R)*-**2b**, *(S)*-**2b**, *(R)*-**2c**, *(S)*-**2c**, *(R)*-**2k**, *(S,R)*-**2m**, *(S,S)*-**2s**, **P4**, and **P5** ([ZIP](#))

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The authors declare no competing financial interest.

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