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Enantioselective Radical Construction of 5-Membered Cyclic Sulfonamides by Metalloradical C–H Amination

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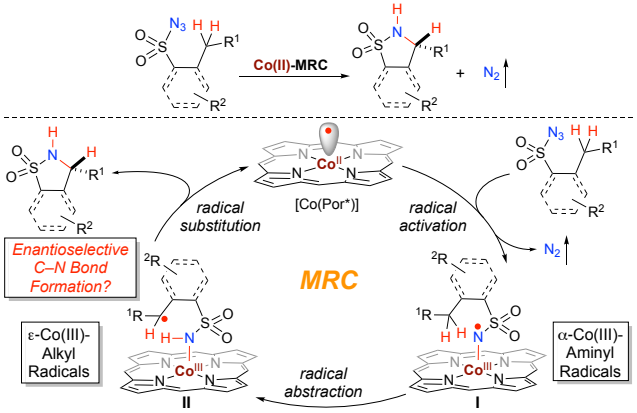
ABSTRACT: Both arylsulfonyl and alkylsulfonyl azides can be effectively activated by the cobalt(II) complexes of D_2-symmetric chiral amidoporphyrins for enantioselective radical 1,5-C–H amination to stereoselectively construct 5-membered cyclic sulfonamides. In addition to C–H bonds with varied electronic properties, the Co(II)-based metalloradical system features chemoselective amination of allylic C–H bonds and is compatible with heteroaryl groups, producing functionalized 5-membered chiral cyclic sulfonamides in high yields with high enantioselectivities. The unique profile of reactivity and selectivity of the Co(II)-catalyzed C–H amination is attributed to its underlying stepwise radical mechanism, which is supported by several lines of experimental evidence.

INTRODUCTION

Radical reactions have been increasingly exploited as new synthetic tools, which are complementary to ionic reactions, for molecular construction of organic compounds.[1] With the aim at addressing the outstanding issues in controlling reactivity and stereoselectivity of radical species,[2] metalloradical catalysis (MRC) has been recently introduced as a conceptually different approach to explore the catalytic application of open-shell metalloradical complexes for both initiation and regulation of homolytic radical reactions.[3,4,5] To this end, cobalt(II) complexes of porphyrins ([Co(Por)]), as stable 15e metalloradicals, have demonstrated the capability of activating organic azides and diazo compounds to generate the fundamentally new α-Co(III)-aminyl radicals and α-Co(III)-alkyl radicals, respectively, upon the release of N_2.[3,6,7] While the N-centered and C-centered organic radicals are stabilized by the Co(III) complexes, they retain the ability to undergo common reactions of free radicals, such as radical addition and H-atom abstraction. More importantly, the reactivity and selectivity of these and subsequent radical reactions can be effectively controlled by the environment of the porphyrin ligands, leading to new catalytic radical processes for stereoselective organic transformations.[8,9,10,11,12] In particular, Co(II)-based metalloradical catalysis (Co(II)-MRC) has been successfully applied to intramolecular radical C–H amination with different types of organic azides as radical precursors.[8] Previously, the Co(II) complex of tetraphenylporphyrin, [Co(TPP)], was shown to catalyze intramolecular C–H amination of arylsulfonyl azides to generate 5-membered cyclic sulfonamides, but required elevated reaction temperature.[8a] Subsequent employment of amidoporphyrins as supporting ligands has enhanced the catalytic activity of the Co(II)-based metalloradical system for intramolecular C–H amination of sulfamoyl azides, even at lower temperature.[8b,8e] This ligand-accelerated catalysis is attributed to the potential hydrogen-bonding interactions between the S=O acceptor of the sulfonyl unit and the N–H donor of the amide moiety of the porphyrin ligand in the α-Co(III)-aminyl radical intermediates.[8b,8e] Assuming the similar ligand acceleration effect, we hoped to enhance the Co(II)-catalyzed system for 1,5-C–H amination of sulfonyl azides by employing amidoporphyrins as supporting ligands (Scheme 1).

Besides arylsulfonyl azides, such enhancement might even enable the activation of the more challenging alkylsulfonyl azides for productive C–H amination. Furthermore, considering the availability of D_2-symmetric chiral amidoporphyrins with tunable electronic, steric and chiral environments,[8e,9b,10a,11a-c] the Co(II)-catalyzed C–H amination could be potentially rendered as an enantioselective radical process (Scheme 1). While the corresponding α-Co(III)-aminyl radical intermediates **I** generated from metalloradical activation of sulfonyl azides were anticipated to undergo 1,5-H-atom abstraction, it was unclear if the two prochiral faces of the C-centered radical in the resulting ε-Co(III)-alkyl radical intermediates **II** could be effectively discriminated for controlling enantioselectivity of the C–N bond formation during the succeeding 5-*exo*-*tet* radical cyclization (Scheme 1). If appropriate chiral amidoporphyrin ligands could be identified to achieve the enantiocontrol, such asymmetric catalytic process for radical C–H amination would be desirable as it allows for stereoselective construction of 5-membered cyclic sulfonamides (also known as sultams), which are both medicinally important and synthetically useful (Figure 1),[13] from readily available sulfonyl azides.

Scheme 1. Intramolecular Radical C(sp^3)–H Amination of Sulfonyl Azides via Co(II)-Based Metalloradical Catalysis



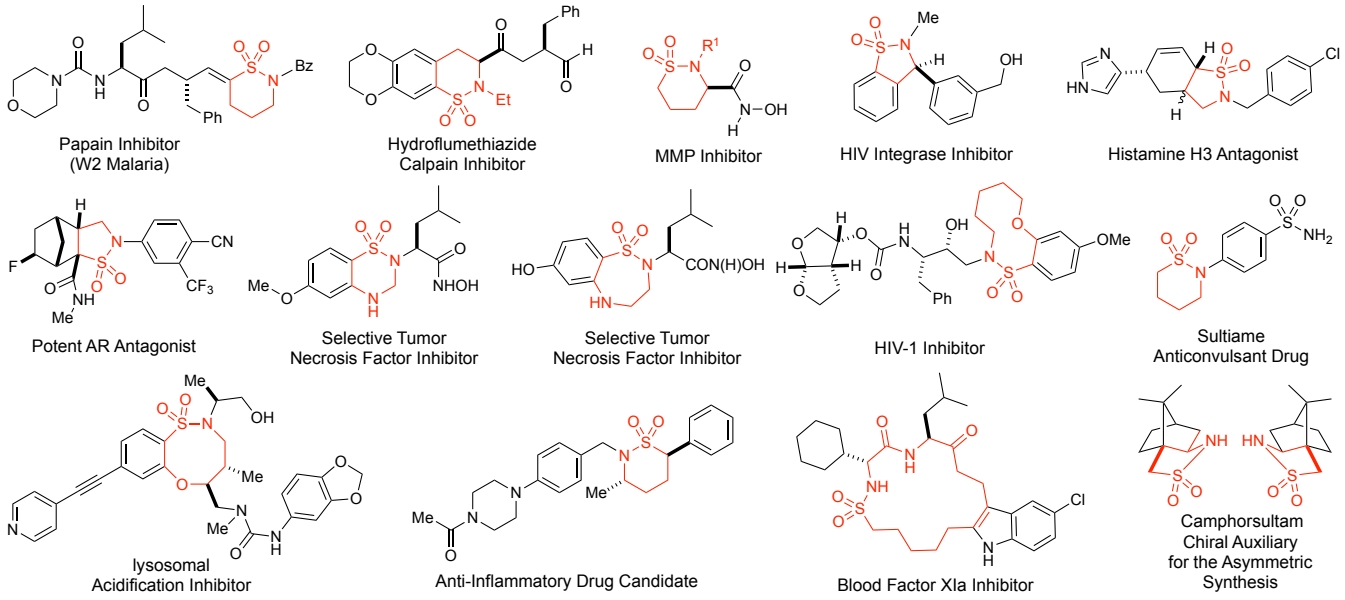


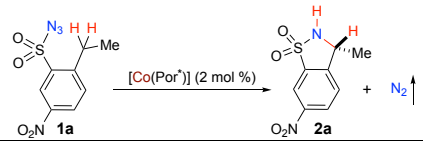
Figure 1. Selective Examples of Bioactive and Synthetically Useful Molecules Containing Cyclic Sulfonamide Motifs.

Catalytic intramolecular C(sp^3)–H amination, especially its enantioselective variant, represents an attractive strategy for the construction of *N*-heterocyclic structures.[14] Despite considerable advancements in recent years,[15,16,17] so far, there are only two previous reports on stereoselective formation of chiral cyclic sulfonamides via asymmetric intramolecular C–H amination.[18] While the first catalytic system based on $Rh(II)_2$ complexes of chiral tetracarboxylates achieved only moderate asymmetric induction,[18a] the more recent Ir(III)-based system with the use of chiral salens could catalyze intramolecular amination of arylsulfonyl azides to form benzofused cyclic sulfonamides with high enantioselectivity.[18b] However, the Ir(III)-catalyzed amination was mainly restricted to arylsulfonyl azides with only one example of cyclic alkylsulfonyl azide.[18b] Evidently, there is still a need to develop new catalytic systems, especially using base metal catalysts, for asymmetric intramolecular C–H amination that is generally applicable for stereoselective synthesis of valuable chiral cyclic sulfonamides with diverse structural features. Herein, we wish to report the development of Co(II) complexes of D_2-symmetric chiral amidoporphyrins ([Co(D_2-Por*)]) as effective metalloradical catalysts for enantioselective radical 1,5-C–H amination of sulfonyl azides. In addition to arylsulfonyl azides, the Co(II)-catalyzed asymmetric system is also applicable to the more challenging alkylsulfonyl azides with different types of C–H bonds, generating chiral 5-membered cyclic sulfonamides in high yields with high enantioselectivities. As additional practical attributes associated with the use of organic azides, the Co(II)-based amination system can be operated under neutral and nonoxidative conditions without the need of any additives, generating the environmentally benign N_2 gas as the only byproduct. Furthermore, we present several lines of experimental evidence that shed light on the unique radical mechanism of this metalloradical system for C–H amination.

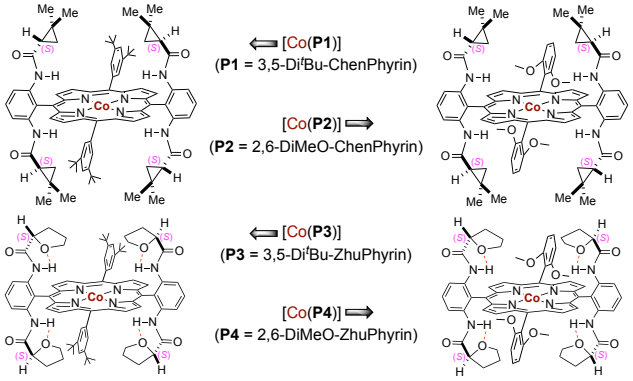
RESULTS AND DISCUSSION

Asymmetric 1,5-C–H Amination of Arylsulfonyl Azides. As the initial efforts for this project, we focused on identification of a suitable D_2-symmetric chiral amidoporphyrin ligand to support the Co(II)-based catalytic system for intramolecular C–H amination with potential asymmetric induction. 2-Ethyl-5-nitrobenzenesulfonyl azide (**1a**), which was shown to be a challenging substrate for the existing Ir(III)-based system because of the presence of the electron-withdrawing nitro group,[18b] was chosen as a test substrate for the Co(II)-based metalloradical system (Table 1). Based on the previously established conditions,[8a] it was found that the first-generation chiral metalloradical catalyst [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-ChenPhyrin)[11a] could effectively catalyze the intramolecular amination reaction of azide **1a**, generating 5-membered benzofused cyclic sulfonamide **2a** as the exclusive product in nearly quantitative yield with low but significant asymmetric induction (Table 1; entry 1). Switching to the catalyst [Co(**P2**)] (**P2** = 2,6-DiMeO-ChenPhyrin) bearing the same chiral amide units but with more sterically-hindered achiral *meso*-aryl groups led to only slight improvement in the enantioselectivity while maintaining the quantitative yield (Table 1; entry 2). On the hypothesis that the low asymmetric induction may be attributed to the relative flexibility of the chiral arms in ChenPhyrin catalysts, we decided to test Co(II) complex of D_2-symmetric chiral amidoporphyrins containing chiral amide units with increased conformational rigidity. Indeed, with the use of [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-ZhuPhyrin) as the catalyst, which was previously shown to possess a more rigid conformation as a result of the unique intramolecular O•••H–N hydrogen-bonding interactions in the (*S*)-(-)-2-tetrahydrofurancarboxamide units,[11b] asymmetric induction was significantly improved without affecting the excellent yield (Table 1; entry 3). Encouraged by the positive outcome, the catalyst [Co(**P4**)] (**P4** = 2,6-DiMeO-ZhuPhyrin),[11b] which incorporates more sterically bulky achiral *meso*-aryl groups into the structure to further enhance the rigidity of the chiral environment, was employed for the amination reaction. Gratifyingly, the desired 1,5-C–H amination product **2a** was produced with 84% ee in still quantitative yield (Table 1; entry 4). The enantioselectivity with [Co(**P4**)] could be further improved by lowering the reaction temperature (Table 1; entries 5 and 6). However, a much lower yield was observed along with the higher enantioselectivity for the reaction at 40 °C (entry 6). Among various solvents screened (see Table S1 in SI), chloroform was identified as the optimal medium for enantioselectivity (Table 1; entry 7). In chloroform, when the reaction was performed at 50 °C with 4 mol % of [Co(**P4**)], the desired benzofused cyclic sulfonamide **2a** was produced in 96% yield with 92% ee (Table 1; entry 8).

Table 1. Ligand Effect on Co(II)-Based Metalloradical System for Asymmetric 1,5-C–H Amination of Arylsulfonyl Azide[a]



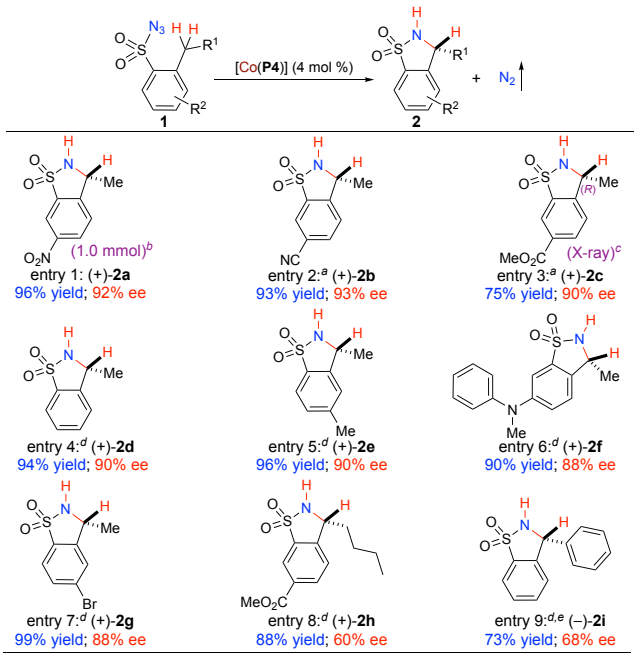
entry	catalyst	temp (°C)	solvent	yield (%)	ee (%)
1	[Co(**P1**)]	80	chlorobenzene	99	28
2	[Co(**P2**)]	80	chlorobenzene	99	32
3	[Co(**P3**)]	80	chlorobenzene	99	49
4	[Co(**P4**)]	80	chlorobenzene	99	84
5	[Co(**P4**)]	60	chlorobenzene	99	86
6	[Co(**P4**)]	40	chlorobenzene	63	88
7	[Co(**P4**)]	60	chloroform	70	89
8[b]	[Co(**P4**)]	50	chloroform	96	92



[a] Reactions were carried out for 18 h on 0.10 mmol scale under N_2; [**1a**] = 0.25 M; Isolated yields; Enantiomeric excess determined by chiral HPLC. [b] 4 mol % catalyst for 48 h.

The metalloradical catalyst [Co(**P4**)] was shown to be generally effective for asymmetric intramolecular C–H amination of various arylsulfonyl azides under the optimized conditions (Table 2). Firstly, it is worth noting that the same high yield and enantioselectivity for formation of benzofused cyclic sulfonamide **2a** could also be obtained when the reaction with **1a** was scaled up 10 times to 1.0 mmol (Table 2; entry 1). In addition to the nitro group, the Co(II)-based metalloradical amination could also be effectively applied to 2-ethylarenesulfonyl azides bearing other electron-withdrawing substituents such as cyano (**1b**) and ester (**1c**) groups, allowing for high-yielding production of functionalized benzofused cyclic sulfonamides **2b** and **2c** in a highly asymmetric manner (Table 2; entries 2 and 3). The absolute configuration of the newly-generated chiral center in **2c** was established as (*R*) by X-ray crystal structural analysis. At a slightly elevated temperature (80 °C), 2-ethylbenzenesulfonyl azide (**1d**) and its derivatives containing different aryl substituents such as electron-donating alkyl (**1e**) and amino (**1f**) groups as well as halogen (**1g**) atoms were also suitable substrates for the amination system, giving the corresponding 5-membered benzofused cyclic sulfonamides **2d**–**2g** in high yields with high enantioselectivities (Table 2; entries 4–7). The complete regioselectivity at the benzylic C–H position by [Co(**P4**)]-catalyzed amination was further highlighted with the high-yielding formation of 5-membered benzofused cyclic sulfonamide **2h** from 2-pentyl-5-(methoxycarbonyl)benzenesulfonyl azide (**1h**), albeit with lower enantioselectivity (Table 2; entry 8). The 6-membered benzofused cyclic sulfonamide from potential amination of the homobenzylic C–H bonds in **1h** was not observed. As expected, C–H bonds at bis-benzylic positions could also be aminated by [Co(**P4**)] as exemplified with the reaction of 2-benzyl benzenesulfonyl azide (**1i**), resulting in formation of the desired **2i**, but in a relatively lower yield with moderate enantioselectivity (Table 2; entry 9).

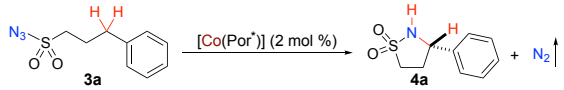
Table 2. [Co(P4)]-Catalyzed Enantioselective 1,5-C–H Amination of Arylsulfonyl Azides[a]



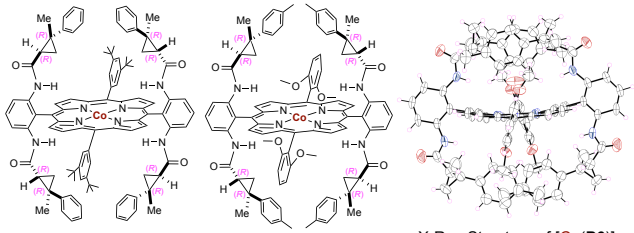
[a] Reactions were carried out in chloroform at 50 °C for 48 h on 0.10 mmol scale under N_2; [**1**] = 0.25 M; Isolated yields; Enantiomeric excess determined by chiral HPLC. [b] 1.0 mmol scale. [c] Absolute configuration determined by X-ray analysis. [d] At 80 °C. [e] In chlorobenzene.

Asymmetric 1,5-C–H Amination of Alkylsulfonyl Azides. Subsequent experiments indicated that asymmetric intramolecular C–H amination of alkylsulfonyl azides behaves differently from arylsulfonyl azides, presumably due to the flexible nature of the linear alkyl chain. As illustrated in Table 3 with substrate 3-phenylpropylsulfonyl azide (**3a**), catalyst [Co(**P4**)] was much less effective in catalyzing the reaction of this alkylsulfonyl azide, affording the 5-membered cyclic sulfonamide **4a** in only 10% yield although with 90% ee (Table 3; entry 1). Catalyst [Co(**P1**)] was found to be much more effective for this reaction, generating **4a** in 97% yield but with only 48% ee (Table 3; entry 2). When the second-generation metalloradical catalyst [Co(**P5**)] (**P5** = 3,5-Di^tBu-QingPhyrin)[11c] was used, the enantioselectivity of this heterocyclization reaction was increased to 69% ee while maintaining an excellent yield of 99%. These results prompted us to develop new metalloradical catalysts with combined features of these existing catalysts. This effort led to the design and synthesis of D_2-symmetric chiral amidoporphyrin 2,6-DiMeO-Qing(4'-Me)Phyrin (**P6**). Its cobalt(II) complex [Co(**P6**)], whose structure was established by X-ray crystallographic analysis, was found to be a superior metalloradical catalyst for asymmetric C–H amination of alkylsulfonyl azide **3a**. The [Co(**P6**)]-catalyzed reaction displayed both high efficiency and excellent stereoselectivity, affording cyclic sulfonamide **4a** in 92% yield with 94% ee (Table 3; entry 4). With [Co(**P6**)] as the optimized catalyst, further solvent evaluation was performed for intramolecular C–H amination of the alkylsulfonyl azide (see Table S2 in Supporting Information (SI)). Among various solvents evaluated, benzene was identified as the optimal medium as it gave the highest enantioselectivity (Table 3; entries 4–6).

Table 3. Ligand Effect on Co(II)-Catalyzed Asymmetric 1,5-C–H Amination of Alkylsulfonyl Azides 3a[a]



entry	catalyst	solvent	yield (%)	ee (%)
1	[Co(**P4**)]	benzene	10	90
2	[Co(**P1**)]	benzene	97	48
3	[Co(**P5**)]	benzene	99	69
4	[Co(**P6**)]	benzene	92	94
5	[Co(**P6**)]	chlorobenzene	95	91
6	[Co(**P6**)]	chloroform	95	84

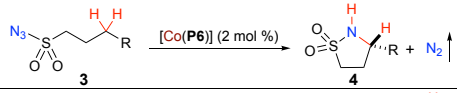


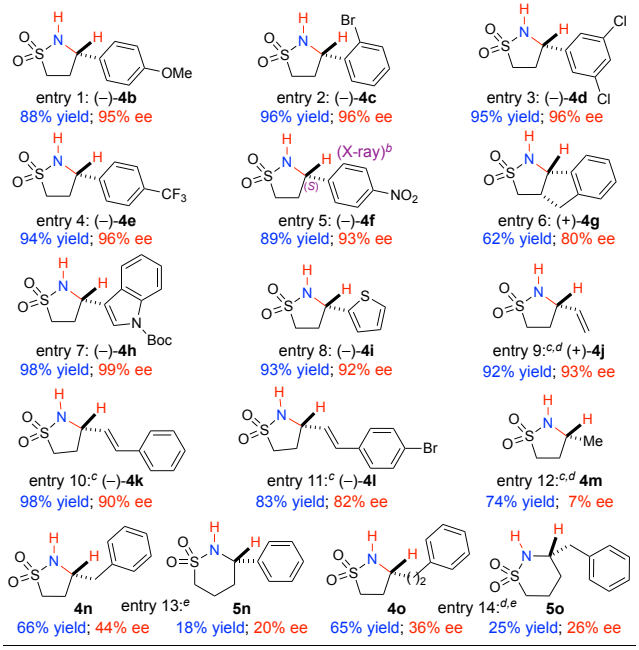
[Co(**P5**)] (**P5** = 3,5-Di^{t}Bu-QingPhyrin) [Co(**P6**)] (**P6** = 2,6-DiMeO-Qing(4'-Me)Phyrin) X-Ray Structure of [Co(**P6**)]

[a] Reactions were carried out at 40 °C for 18 h on 0.25 mmol scale under N_2; [**3a**] = 0.10 M; Isolated yields; Enantiomeric excess determined by chiral HPLC.

The new metalloradical catalyst [Co(**P6**)] proved to be generally effective for asymmetric intramolecular C–H amination of alkylsulfonyl azides as demonstrated with reactions of different propylsulfonyl azide derivatives **3** under the optimized conditions (Table 4). Like the amination reaction of **3a**, the [Co(**P6**)]-based catalytic system performed equally well for 3-arylpropylsulfonyl azides **3b**–**3c** with various aryl substituents at the *ortho*-, *meta*- or *para*-positions, producing the corresponding 5-membered cyclic sulfonamides **4b**–**4c** in high yields with excellent enantioselectivities (Table 4; entries 1–3). Resembling the [Co(**P4**)]-based catalytic system for arylsulfonyl azides **1** (Table 2), the [Co(**P6**)]-catalyzed amination could also be applicable for electron-deficient C–H bonds, as exemplified with enantioselective formation of the desired cyclic sulfonamides **4e** and **4f** from azide substrates bearing electron-withdrawing aryl substituents such as trifluoromethyl (**3e**) and nitro (**3f**) groups (Table 4; entries 4–5). The absolute configuration of the newly-generated chiral center in cyclic sulfonamide **4f** was established as (*S*) by X-ray crystal structural analysis. Additionally, indane-derived substrate **3g** was successfully desymmetrized by [Co(**P6**)]-based amination to give *cis*-fused cyclic sulfonamide **4g** in moderate yield with good enantioselectivity (Table 4; entry 6). Alkylsulfonyl azides derived from indole (**3h**) and thiophene (**3i**) could also be intramolecularly aminated to furnish the desired heteroarene-containing cyclic sulfonamides **4h** and **4i**, respectively (Table 4; entries 7 and 8). Furthermore, the Co(II)-based system was shown to be capable of catalyzing intramolecular amination of allylic C–H bonds chemoselectively without any complication from the competitive intramolecular aziridination of C=C bonds. For example, sulfonyl azides **3j**–**3l** derived from both terminal and internal olefins could be chemoselectively aminated at the allylic C–H positions, providing the corresponding vinyl-substituted cyclic sulfonamides **4j**–**4l** in high yields with high enantioselectivities (Table 4; entries 9–11). The [Co(**P6**)]-based system could be also extended for amination of non-activated C–H substrates such as sulfonyl azides **3m**–**3o**, affording the 5-membered cyclic sulfonamides **4m**–**4o** in good yields (Table 4; entries 12–14). While the asymmetric induction was low for these reactions, the enantioselectivities of **4n** and **4o** were significantly higher than **4m**, indicating the positive effect of distal phenyl substituent. More importantly, the formation of 5-membered cyclic sulfonamide **4n** as the major products (66% yield) with the 6-membered cyclic sulfonamide **5n** as the minor product (18% yield) from the reaction of azide **3n** illustrated that the metalloradical catalyst [Co(**P6**)] could regioselectively aminate the stronger homobenzylic over the weaker benzylic C–H bonds (Table 4; entry 13). The regioselective amination of stronger (bishomobenzylic) over weaker C–H bonds (homobenzylic and benzylic) by [Co(**P6**)] was also clearly demonstrated from the formation of 5-membered cyclic sulfonamide **4o** as the major product (65% yield) with the 6-membered cyclic sulfonamide **5o** as the minor product (25% yield) without observation of any 7-membered product from the reaction of azide **3o** (Table 4; entry 14). This remarkable regioselectivity indicated that the corresponding α-Co(III)-aminyl radicals **I** (Scheme 1) inside the catalyst [Co(**P6**)] was positioned to have a kinetic preference for 1,5- over 1,6- and 1,7-H abstraction.

Table 4. [Co(P6)]-Catalyzed Enantioselective 1,5-C–H Amination of Alkylsulfonyl Azides[a]





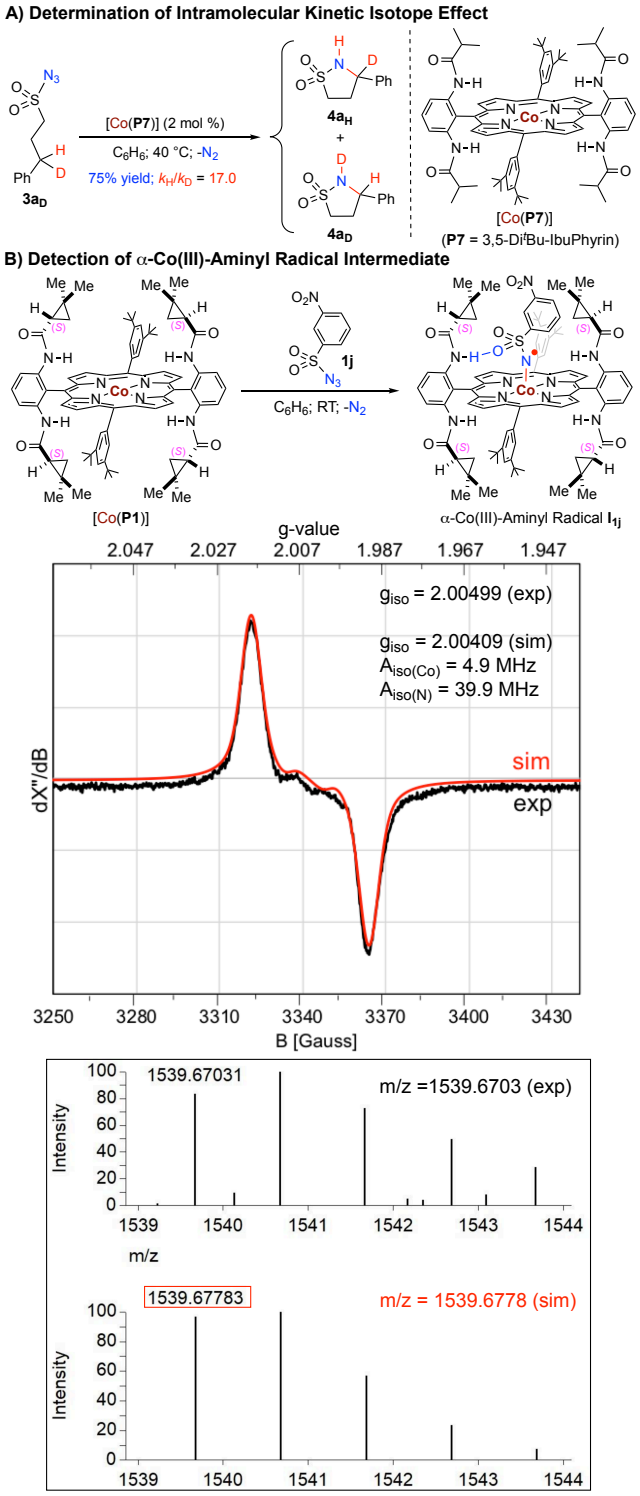
[a] Reactions were carried out in benzene at 40 °C for 18 h on 0.25 mmol scale under N_2; [**3**] = 0.10 M; Isolated yields; Enantiomeric excess determined by chiral HPLC. [b] Absolute configuration determined by X-ray analysis. [c] Carried out on 0.10 mmol scale at 0 °C for 24 h using 5 mol % [Co(**P6**)] in PhCl. [d] Enantiomeric excess determined via derivatization. [e] Carried out for 48 h.

Mechanistic Studies of 1,5-C–H Amination of Sulfonyl Azides. The profile of reactivity and selectivity exhibited by the Co(II)-based system for 1,5-C–H amination is consistent with the proposed stepwise radical mechanism that involves the α-Co(III)-aminyl radicals **I** and ε-Co(III)-alkyl radicals **II** as the key intermediates (Scheme 1).[6] To obtain direct evidence for the proposed mechanism, a set of mechanistic experiments was carried out (Scheme 2). First, mono-deuterated 3-phenylpropylsulfonyl azide **3a$_D$** was used as the substrate to determine the kinetic isotopic effect (KIE) for the Co(II)-catalyzed intramolecular C–H amination (Scheme 2A). Using the Co(II) complex of D_{2h}-symmetric amidoporphyrin 3,5-Di^{t}Bu-IbuPhyrin,[9a] [Co(**P7**)], as an achiral catalyst, the reaction of azide

3a$_D$ provided a mixture of cyclic sulfonamides **4a$_H$** and **4a$_D$**, which resulted from 1,5-C–H and 1,5-C–D amination, respectively, in 75% combined yield. Analysis of the product mixture by ^{1}H-NMR provided a value of 17.0 for intramolecular KIE. This high value of primary KIE agrees well with the proposed step of C–H bond cleavage via H-atom abstraction by α-Co(III)-aminyl radical intermediate **I** (Scheme 1). Furthermore, in an effort to directly detect the radical intermediate **I**, 3-nitrobenzenesulfonyl azide (**1j**), which resembles azide **1a** but lacks C(sp^3)–H bonds for further H-atom abstraction, was chosen to react with [Co(**P1**)] for the generation of the corresponding α-Co(III)-aminyl radical **I$_{1j}$** (Scheme 2B). The isotropic EPR spectrum of the reaction solution of [Co(**P1**)] with **1j** was recorded at room temperature (Scheme 2B; see SI for details), displaying the well-resolved signals that are characteristic of α-Co(III)-aminyl radicals.[6a-b] In accord with the spin translocation from the Co(II) ion to the N atom during the step of metalloradical activation of the azide (Scheme 1), the observed isotropic g value of 2.00499 evidently indicated the existence of organic radicals. Furthermore, the experimental spectrum could be fittingly simulated on the basis of couplings by both ^{14}N (I = 1) and ^{59}Co (I = 7/2) with hyperfine coupling constants of 39.9 MHz and 4.9 Hz, respectively. Moreover, α-Co(III)-aminyl radical **I$_{1j}$** from the reaction mixture of [Co(**P1**)] with azide **1j** could also be detected by high-resolution mass spectrometry (HRMS) with ESI ionization. The obtained spectrum (Scheme 2B; see SI for details) clearly revealed a signal corresponding to [Co(**P1**)(NSO$_2$C$_6$H$_4$NO$_2$)]$^+$ (m/z = 1539.6703), which resulted from the neutral α-Co(III)-aminyl radical **I$_{1j}$** by the loss of one electron. Both the exact mass and the pattern of isotope distribution determined by ESI-HRMS matched nicely with those calculated from the formula [Co(**P1**)(NSO$_2$C$_6$H$_4$NO$_2$)]$^+$.

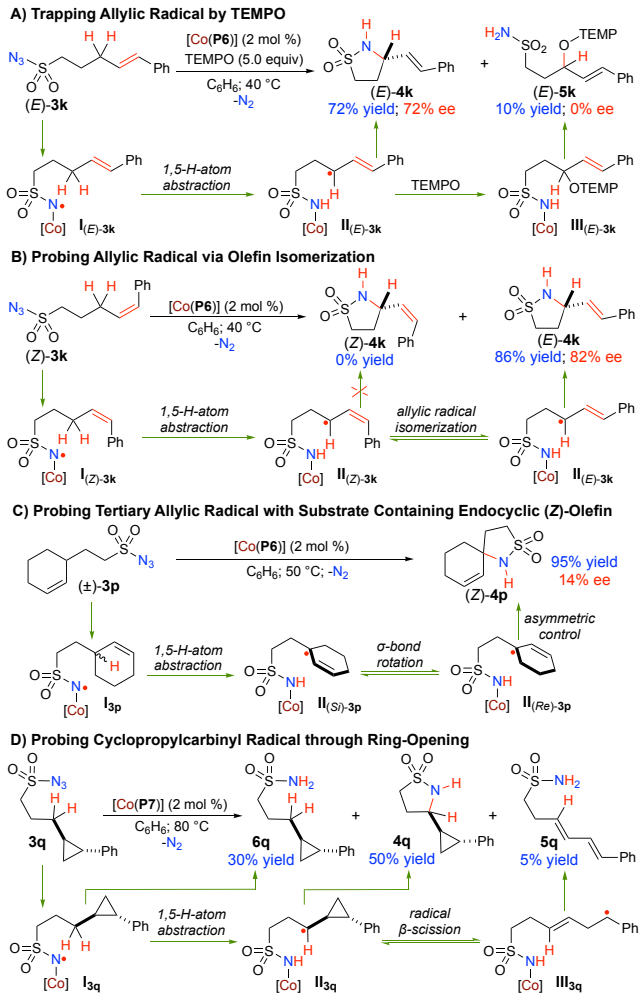
Further experiments were designed to trap and probe the ε-Co(III)-alkyl radical intermediates **II** generated from the subsequent step of 1,5-H-atom abstraction by α-Co(III)-aminyl radical intermediates **I** (Scheme 1). To this end, the amination of allylic C–H bonds of azide (*E*)-**3k** by [Co(**P6**)] was performed in the presence of TEMPO (Scheme 3A). Remarkably, even in the presence of a large excess of TEMPO (5.0 equiv), the 5-membered cyclic sulfonamide (*E*)-**4k** was still produced as the major product in 72% yield, indicating highly facile formation of the C–N bond via *5-exo-tet* radical cyclization of ε-Co(III)-allylic radical **II**$_{(E)\text{-}3k}$. Concomitantly, the reaction produced (*E*)-**5k** as a minor product in 10% yield, which was presumably formed from the TEMPO-trapped intermediate **III**$_{(E)\text{-}3k}$. The fact that there was no asymmetric induction in (*E*)-**5k** while observing significant enantioselectivity for (*E*)-**4k** in 72% ee indicates markedly different environment for the C–O and C–N bond formation processes. The existence of ε-Co(III)-allylic radical intermediates **II** could be further probed via olefin isomerization during the catalytic reaction of azide (*Z*)-**3k** by [Co(**P6**)] (Scheme 3B). Like the reaction of (*E*)-**3k**, the 1,5-amination of allylic C–H bonds of (*Z*)-**3k** resulted in exclusive formation of (*E*)-**4k** in 86% yield with 82% ee without forming any (*Z*)-**4k**, representing a rare example of enantioselective allylic C–H amination with diastereoconvergence. This result suggests that the C–N bond formation via *5-exo-tet* radical cyclization occurred much faster in the isomerized radical **II**$_{(E)\text{-}3k}$ than the initially-formed ε-Co(III)-allylic radical **II**$_{(Z)\text{-}3k}$, presumably due to the steric difference between the (*E*)- and (*Z*)-olefin units. When the cyclohexene-based azide **3p** that contains an endocyclic (*Z*)-olefin was employed as the substrate, the 1,5-amination of the racemic tertiary allylic C–H bond could be effectively catalyzed by [Co(**P6**)] to afford the spirobicyclic product (*Z*)-**4p** in an excellent yield (Scheme 3C). While the (*Z*)-configuration of the olefin was retained owing to incapable isomerization of the locked endocyclic C=C bond, the fact that (*Z*)-**4p** was obtained in 95% yield with low but significant enantioselectivity (14% ee) implies the intermediacy of the tertiary allylic radicals **II**$_{(Si)\text{-}3p}$ and **II**$_{(Re)\text{-}3p}$ resulted from 1,5-H-atom abstraction from the racemic tertiary C–H bond. Furthermore, the catalytic reaction of azide **3q** by [Co(**P7**)] was performed to probe the existence of the corresponding ε-Co(III)-alkyl radical **II$_{3q}$** through ring-opening (Scheme 3D). Besides the construction of cyclic

Scheme 2. Kinetic Isotope Effect of Catalytic 1,5-C–H Amination and Spectroscopic Detection of α-Co(III)-Aminyl Radical



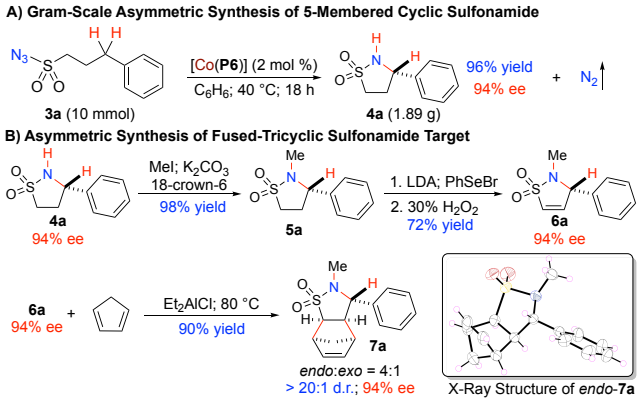
sulfonamide **4q** in 50% yield from ε-Co(III)-alkyl radical $\mathbf{II_{3q}}$, the reaction produced sulfonamide **6q** in 30% yield directly from α-Co(II)-aminyl radical $\mathbf{I_{3q}}$. Additionally, detailed analysis of the reaction mixture by ^{1}H NMR revealed the formation of acyclic sulfonamide **5q** as the third product in 5% yield. The identity of product **5q** was further confirmed through an independent synthesis (see SI). Compound **5q** was likely originated from homoallylic radical intermediate $\mathbf{III_{3q}}$ that was generated from ring-opening of the cyclopropylcarbinyl radical $\mathbf{II_{3q}}$. Collectively, these experimental results (Schemes 2 and 3) provided convincing evidences for the proposed stepwise radical mechanism of the Co(II)-catalyzed 1,5-C–H amination of sulfonyl azides (Scheme 1).

Scheme 3. Trapping and Probing of ε-Co(III)-Alkyl Radicals after 1,5-H-Atom Abstraction in Co(II)-Catalyzed Amination



Scalability and Utility of Co(II)-Catalyzed Asymmetric 1,5-C–H Amination of Sulfonyl Azides. The successful development of asymmetric intramolecular C–H amination of both arylsulfonyl and alkylsulfonyl azides via Co(II)-based metalloradical catalysis provides a practical method to access optically active cyclic sulfonamides bearing various functionalities, which should find applications in research and development of pharmaceuticals. To demonstrate the practicality of the Co(II)-based system for 1,5-C–H amination, the catalytic reaction of 3-phenylpropylsulfonyl azide (**3a**) by [Co(**P6**)] was scaled up 40 times from 0.25 mmol to 10 mmol under the identical conditions (Scheme 4A). The desired 5-membered cyclic sulfonamide **4a** was produced in multigram quantities in 96% yield with 94% ee, which was similar to those (92% yield; 94% ee) obtained from the corresponding small-scale reaction (Table 3; entry 4). To showcase its synthetic utility, the resulting enantioenriched cyclic sulfonamide **4a** was employed as the key chiral synthon for the synthesis of compound **7a** in view of recent attention to the broad enzyme inhibitory properties of enantiopure fused-cyclic sulfonamides.[13,19] As depicted in Scheme 4B, the fused-tricyclic sulfonamide **7a** could be effectively synthesized from **4a** through a 4-step sequence of *N*-methylation,[13m] selenylation,[20] elimination[21] and Diels-Alder reactions[22] in an overall 64% yield without the erosion of the original enantiomeric purity. The stereochemistry of the *endo*-stereoisomer **7a** was unambiguously established by X-ray structural analysis (Scheme 4B).

Scheme 4. Applications of Co(II)-Catalyzed Enantioselective 1,5-C–H Amination of Sulfonyl Azides



CONCLUSIONS

In summary, we have developed Co(II)-based metalloradical systems for asymmetric 1,5-C–H amination of both arylsulfonyl and alkylsulfonyl azides under neutral and nonoxidative conditions. In addition to benzylic C–H bonds with varied steric and electronic properties, the Co(II)-catalyzed enantioselective radical amination is highlighted with chemoselective amination of allylic C–H bonds as well as compatibility with heteroaryl groups, allowing for stereoselective construction of functionalized 5-membered cyclic sulfonamides in high yields with excellent enantioselectivities. This work represents, to date, one of the most general and selective catalytic systems for asymmetric intramolecular C–H amination of sulfonyl azides. The unique profile of reactivity and selectivity of the Co(II)-based asymmetric 1,5-C–H amination is attributed to the underlying stepwise radical mechanism, which is well supported by several lines of experimental evidence. Practically, we have demonstrated the Co(II)-based radical C–H amination protocol can be operated on a multigram-scale under the same mild conditions without affecting the high yield and excellent enantioselectivity. To showcase its synthetic utility, the Co(II)-catalyzed enantioselective radical amination has been applied as the key step for the highly effective synthesis of the fused-tricyclic sulfonamide molecule.

ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental details, supplementary figures and spectroscopic data (pdf)

Crystallography data for **2c**, [Co(**P6**)], **4f** and *endo*-**7a** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For select books, see: (a) Chatgilialoglu, C.; Studer, A. *Encyclopedia of Radicals in Chemistry, Biology and Materials*; John Wiley & Sons, 2012. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; John Wiley & Sons, 2008. (c) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, 2003. For recent reviews, see: (d) Studer, A.; Curran, D. P. Catalysis of Radical Reactions: A Radical Chemistry Perspective. *Angew. Chem., Int. Ed*. **2016**, *55*, 58–102. (e) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. Enantioselective Catalysis of Photochemical Reactions. *Angew. Chem., Int. Ed*. **2015**, *54*, 3872–3890. (f) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev*. **2013**, *113*, 5322–5363. (g) Quiclet-Sire, B.; Zard, S. Z. Fun with Radicals: Some New Perspectives for Organic Synthesis. *Pure. Appl. Chem.* **2011**, *83*, 519–551. (h) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev*. **2011**, *40*, 102–113. (i) Zard, S. Z. Recent Progress in the Generation and Use of Nitrogen-Centred Radicals. *Chem. Soc. Rev*. **2008**, *37*, 1603–1618.

(2) For select examples on approaches to control radical reactivity and stereoselectivity, see: (a) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. A Dual-Catalysis Approach to Enantioselective [2 + 2] Photocycloadditions Using Visible Light. *Science* **2014**, *344*, 392–396. (b) Huo, H. H.; Shen, X. D.; Wang, C. Y.; Zhang, L. L.; Röse, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. Asymmetric Photoredox Transition-Metal Catalysis Activated by Visible Light. *Nature* **2014**, *515*, 100–103. (c) Hoyt, J. M.; Schmidt, V. A.; Tondreau, A. M.; Chirik, P. J. Iron-Catalyzed Intermolecular [2+2] Cycloadditions of Unactivated Alkenes. *Science* **2015**, *349*, 960–693. (d) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C-N Cross-Couplings Induced by Visible Light. *Science* **2016**, *351*, 681–684. (e) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective Cyanation of Benzylic C–H Bonds via Copper-Catalyzed Radical Relay. *Science* **2016**, *353*, 1014–1018. (f) Funken, N.; Mühlhaus, F.; Gansäuer, A. General, Highly Selective Synthesis of 1,3- and 1,4-Difunctionalized Building Blocks by Regiodivergent Epoxide Opening. *Angew. Chem., Int. Ed.* **2016**, *55*, 12030–12034. (g) Brill, Z. G.; Grover, H. K.; Maimone, T. J. Enantioselective Synthesis of an Ophiobolin Sesterterpene via a Programmed Radical Cascade. *Science* **2016**, *352*, 1078–1082. (h) Kern, N.; Plesniak, M. P.; McDouall, J. J. W.; Procter, D. J. Enantioselective Cyclizations and Cyclization Cascades of Samarium Ketyl Radicals. *Nat. Chem.* **2017**, *9*, 1198–1204. (i) Morrill, C.; Jensen, C.; Just-Baringo, X.; Grogan, G.; Turner, N. J.; Procter, D. J. Biocatalytic Conversion of Cyclic Ketones Bearing α-Quaternary Stereocenters into Lactones in an Enantioselective Radical Approach to Medium-Sized Carbocycles. *Angew. Chem. Int. Ed.* **2018**, 57, 3692–3696. (j) Huang, H.-M.; McDouall, J. J. W.; Procter, D. J. SmI_2-Catalysed Cyclization Cascades by Radical Relay. *Nat. Catal.* **2019**, *2*, 211–218.

(3) For select reviews and highlights on Co(II)-based MRC, see: (a) Huang, H.-M.; Garduño-Castro, M. H.; Morrill, C.; Procter, D. J. Catalytic Cascade Reactions by Radical Relay. *Chem. Soc. Rev.* **2019**. *48*, 4626–4638. (b) Demarteau, J.; Debuigne, A.; Detrembleur, C. Organocobalt Complexes as Sources of Carbon-Centered Radicals for Organic and Polymer Chemistries. *Chem. Rev.* **2019**, *119*, 6906–6955. (c) Singh, R.; Mukherjee, A., Metalloporphyrin Catalyzed C–H Amination. *ACS Catalysis* **2019**, *9*, 3604–3617. (d) Pellissier, H.; Clavier, H. Enantioselective Cobalt-Catalyzed Transformations. *Chem. Rev*. **2014**, *114*, 2775–2823. (e) Che, C. M.; Lo, V. K. Y.; Zhou, C. Y.; Huang, J. S. Selective Functionalisation of Saturated C–H Bonds with Metalloporphyrin Catalysts. *Chem. Soc. Rev*. **2011**, *40*, 1950–1975. (f) Driver, T. G. Recent Advances in Transition Metal-Catalyzed N-Atom Transfer Reactions of Azides. *Org. Biomol. Chem*. **2010**, *8*, 3831–3846. (g) Fantauzzi, S.; Caselli, A.; Gallo, E. Nitrene Transfer Reactions Mediated by Metalloporphyrin Complexes. *Dalton Trans*. **2009**, 5434–5443. (h) Doyle, M. P. Exceptional Selectivity in Cyclopropanation Reactions Catalyzed by Chiral Cobalt(II)–Porphyrin Catalysts. *Angew. Chem., Int. Ed*. **2009**, *48*, 850–852.

(4) For select examples of Ti(III)-based radical processes, see: (a) Nugent, W. A.; RajanBabu, T. V. Titanium(III)-Induced Cyclization of Epoxy Olefins. *J. Am. Chem. Soc*. **1988**, *110*, 8561–8562. (b) RajanBabu, T. V.; Nugent, W. A. Selective Generation of Free Radicals from Epoxides Using a Transition-Metal Radical. A Powerful New Tool for Organic Synthesis. *J. Am. Chem. Soc*. **1994**, *116*, 986–997. (c) Gansäuer, A.; Rinker, B.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. A Radical Tandem Reaction with Homolytic Cleavage of a Ti–O Bond. *Angew. Chem., Int. Ed*. **2003**, *42*, 3687–3690. (d) Gansäuer, A.; Fan, C.-A.; Keller, F.; Keil, J. Titanocene-Catalyzed Regiodivergent Epoxide Openings. *J. Am. Chem. Soc*. **2007**, *129*, 3484–3485. (e) Gansäuer, A.; Fleckhaus, A.; Lafont, M. A.; Okkel, A.; Kotsis, K.; Anoop, A.; Neese, F. Catalysis via Homolytic Substitutions with C−O and Ti−O Bonds: Oxidative Additions and Reductive Eliminations in Single Electron Steps. *J. Am. Chem. Soc*. **2009**, *131*, 16989–16999. (f) Gansäuer, A.; Hildebrandt, S.; Michelmann, A.; Dahmen, T.; von Laufenberg, D.; Kube, C.; Fianu, G. D.; Flowers II, R. A. Cationic Titanocene(III) Complexes for Catalysis in Single-Electron Steps. *Angew. Chem., Int. Ed*. **2015**, *54*, 7003–7006. (g) Gansäuer, A.; Hildebrandt, S.; Vogelsang, E.; Flowers II, R. A. Tuning the redox properties of the Titanocene(III)/(IV)-Couple for Atom-Economical Catalysis in Single Electron Steps. *Dalton Trans*. **2016**, *45*, 448–452. (h) Hao, W.; Wu, X.; Sun, J. Z.; Siu, J. C.; MacMillan, S. N.; Lin, S. Radical Redox-Relay Catalysis: Formal [3+2] Cycloaddition of N-Acylaziridines and Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 12141–12144. (i) Yao, C.; Dahmen, T.; Gansäuer, A.; Norton, J. Anti-Markovnikov Alcohols via Epoxide Hydrogenation through Cooperative Catalysis. *Science* **2019**, *364*, 764–767. (j) Ye, K.-Y.; McCallum, T.; Lin, S. Bimetallic Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 9548–9554.

(5) For select examples of catalytic radical processes involving metalloradical intermediates, see: (a) Smith, D. M.; Pulling, M. E.; Norton, J. R. Tin-Free and Catalytic Radical Cyclizations. *J. Am. Chem. Soc.* **2007**, *129*, 770–771. (b) Estes, D. P.; Norton, J. R.; Jockusch, S.; Sattler, W. Mechanisms by which Alkynes React with $CpCr(CO)_3H$. Application to Radical Cyclization. *J. Am. Chem. Soc.* **2012**, *134*, 15512–15518. (c) Li, G.; Han, A.; Pulling, M. E.; Estes, D. P.; Norton, J. R. Evidence for Formation of a Co–H Bond from $(H_2O)_2Co(dmgBF_2)_2$ under H_2: Application to Radical Cyclizations. *J. Am. Chem. Soc.* **2012**, *134*, 14662–14665. (d) Kuo, J. L.; Hartung, J.; Han, A.; Norton, J. R. Direct Generation of Oxygen-Stabilized Radicals by H• Transfer from Transition Metal Hydrides. *J. Am. Chem. Soc.* **2015**, *137*, 1036–1039.

(6) For detailed studies on the radical mechanism of [Co(Por)]-catalyzed C–H amination, including EPR observation of α-Co(III)-aminyl radical intermediates (also known as Co(III)-nitrene radicals), see: (a) Lyaskovskyy, V.; Olivos Suarez, A. I.; Lu, H.; Jiang, H.;

Zhang, X. P.; de Bruin, B. Mechanism of Cobalt(II) Porphyrin-Catalyzed C–H Amination with Organic Azides: Radical Nature and H-Atom Abstraction Ability of the Key Cobalt(III)–Nitrene Intermediates. *J. Am. Chem. Soc.* **2011**, *133*, 12264–12273. (b) Goswami, M.; Lyaskovskyy, V.; Domingos, S. R.; Buma, W. J.; Woutersen, S.; Troeppner, O.; Ivanović-Burmazović, I.; Lu, H.; Cui, X.; Zhang, X. P.; Reijerse, E. J.; DeBeer, S.; van Schooneveld, M. M.; Pfaff, F. F.; Ray, K.; de Bruin, B. Characterization of Porphyrin-Co(III)-'Nitrene Radical' Species Relevant in Catalytic Nitrene Transfer Reactions. *J. Am. Chem. Soc.* **2015**, *137*, 5468–5479. For related DFT studies on the radical mechanism of [Co(Por)]-catalyzed olefin aziridination and ligand hydrogen-bonding effect, see: (c) Hopmann, K. H.; Ghosh, A. Mechanism of Cobalt-Porphyrin–Catalyzed Aziridination. *ACS Catal.* **2011**, *1*, 597–600.

(7) For detailed studies on the radical mechanism involving α-Co(III)-alkyl radical intermediates (also known as Co(III)-carbene radicals), see: (a) Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. 'Carbene Radicals' in Co^{II}(por)-Catalyzed Olefin Cyclopropanation. *J. Am. Chem. Soc.* **2010**, *132*, 10891–10902. (b) Lu, H.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. Experimental Evidence for Cobalt(III)-Carbene Radicals: Key Intermediates in Cobalt(II)-Based Metalloradical Cyclopropanation. *J. Am. Chem. Soc.* **2011**, *133*, 8518–8521.

(8) For select examples of radical C–H amination via Co(II)-based MRC, see: (a) Ruppel, J. V.; Kamble, R. M.; Zhang, X. P. Cobalt-Catalyzed Intramolecular C−H Amination with Arylsulfonyl Azides. *Org. Lett.* **2007**, *9*, 4889−4892. (b) Lu, H.; Jiang, H.; Wojtas, L. Zhang, X. P. Selective Intramolecular C–H Amination through the Metalloradical Activation of Azides: Synthesis of 1,3-Diamines under Neutral and Nonoxidative Conditions. *Angew. Chem., Int. Ed*. **2010**, *49*, 10192–10196. (c) Zardi, P.; Intrieri, D.; Caselli, A.; Gallo, E. Co(porphyrin)-Catalysed Amination of 1,2-Dihydronaphthalene Derivatives by Aryl Azides. *J. Organomet. Chem*. **2012**, *716*, 269–274. (d) Kuijpers, P. F.; Tiekink, M. J.; Breukelaar, W. B.; Broere, D. L. J.; van Leest, N. P.; van der Vlugt, J. I.; Reek, J. N. H.; de Bruin, B. Cobalt-Porphyrin-Catalysed Intramolecular Ring-Closing C−H Amination of Aliphatic Azides: A Nitrene-Radical Approach to Saturated Heterocycles. *Chem. Eur. J.* **2017**, *23*, 7945–7952. For select example on asymmetric radical C–H amination via Co(II)-MRC, see: (e) Lang, K.; Torker, S.; Wojtas, L.; Zhang, X. P. Asymmetric Induction and Enantiodivergence in Catalytic Radical C–H Amination via Enantiodifferentiative H-Atom Abstraction and Stereoretentive Radical Substitution. *J. Am. Chem. Soc.* **2019**. *141*, 12388–12396.

(9) For select examples of radical olefin aziridination via Co(II)-based MRC, see: (a) Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, X. P. A Highly Effective Cobalt Catalyst for Olefin Aziridination with Azides: Hydrogen Bonding Guided Catalyst Design. *Org. Lett.* **2008**, *10*, 1995–1998. (b) Jiang, H.; Lang, K.; Lu, H.; Wojtas, L.; Zhang, X. P. Asymmetric Radical Bicyclization of Allyl Azidoformates via Cobalt(II)-Based Metalloradical Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 9164–9167.

(10) For select examples of radical C–H alkylation via Co(II)-based MRC, see: (a) Wang, Y.; Wen, X.; Cui, X.; Zhang, X. P. Enantioselective Radical Cyclization for Construction of 5-Membered Ring Structures by Metalloradical C–H Alkylation. *J. Am. Chem. Soc.* **2018**, *140*, 4792–4796. (b) Karns, A. S.; Goswami, M.; de Bruin, B. Catalytic Synthesis of Indolines by Hydrogen Atom Transfer to Cobalt(III)-Carbene Radicals. *Chem. -Eur. J.* **2018**, *24*, 5253–5258.

(11) For select examples of radical olefin cyclopropanation via Co(II)-based MRC, see: (a) Chen, Y.; Fields, K. B.; Zhang, X. P. Bromoporphyrins as Versatile Synthons for Modular Construction of Chiral Porphyrins: Cobalt-Catalyzed Highly Enantioselective and Diastereoselective Cyclopropanation. *J. Am. Chem. Soc.* **2004**, *126*, 14718–14719. (b) Zhu, S.; Ruppel, J. V.; Lu, H.; Wojtas, L.; Zhang, X. P. Cobalt-Catalyzed Asymmetric Cyclopropanation with Diazosulfones: Rigidification and Polarization of Ligand Chiral Environment via Hydrogen Bonding and Cyclization. *J. Am. Chem. Soc.* **2008**, *130*, 5042–5043. (c) Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; Lopez de Mesa, S.; Wojtas, L.; Zhang, X. P. Highly Asymmetric Intramolecular Cyclopropanation of Acceptor-Substituted Diazoacetates by Co(II)-Based Metalloradical Catalysis: Iterative Approach for Development of New-Generation Catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 15292–15295. (d) Reddy, A. R.; Hao, F.; Wu, K.; Zhou, C.-Y.; Che, C. M. Cobalt(II) Porphyrin-Catalyzed Intramolecular Cyclopropanation of N-Alkyl Indoles/Pyrroles with Alkylcarbene: Efficient Synthesis of Polycyclic N-Heterocycles. *Angew. Chem., Int. Ed*. **2016**, *55*, 1810–1815. (e) Goswami, M.; de Bruin, B.; Dzik, W. I. Difluorocarbene Transfer from a Cobalt Complex to an Electron-Deficient Alkene. *Chem. Commun.* **2017,** *53*, 4382–4385. (f) Chirila, A.; Gopal Das, B.; Paul, N. D.; de Bruin, B. Diastereoselective Radical-Type Cyclopropanation of Electron-Deficient Alkenes Mediated by the Highly Active Cobalt(II) Tetramethyltetraaza[14]annulene Catalyst. *ChemCatChem* **2017**, *9*, 1413–1421. (g) Roy, S.; Das, S. K.; Chattopadhyay, B. Cobalt(II)-based Metalloradical Activation of 2-(Diazomethyl)pyridines for Radical Transannulation and Cyclopropanation. *Angew. Chem., Int. Ed.* **2018**, 57, 2238–2243.

(12) For other transformations via MRC, see: (a) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. Regioselective Synthesis of Multisubstituted Furans via Metalloradical Cyclization of Alkynes with alpha-Diazocarbonyls: Construction of Functionalized alpha-Oligofurans. *J. Am. Chem. Soc.* **2012**, *134*, 19981–19984. (b) Paul, N. D.; Mandal, S.; Otte, M.; Cui, X.; Zhang, X. P.; de Bruin, B. Metalloradical Approach to 2H-Chromenes. *J. Am. Chem. Soc.* **2014**, *136*, 1090–1096. (c) Das, B. G.; Chirila, A.; Tromp, M.; Reek, J. N. H.; de Bruin, B. Co^{III}-Carbene Radical Approach to Substituted 1H-Indenes. *J. Am. Chem. Soc.* **2016**, *138*, 8968–8975. (d) Gu, Z.-Y.; Liu, Y.; Wang, F.; Bao, X.; Wang, S.-Y.; Ji, S.-J. Cobalt(II)-Catalyzed Synthesis of Sulfonyl Guanidines via Nitrene Radical Coupling with Isonitriles: A Combined Experimental and Computational Study. *ACS Catalysis* **2017**, *7*, 3893–3899. (e) Liu, J.; Hu, L.; Wang, L.; Chen, H.; Deng, L. An Iron(II) Ylide Complex as a Masked Open-Shell Iron Alkylidene Species in Its Alkylidene-Transfer Reactions with Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 3876–3888. (f) Roy, S.; Khatua, H.; Das, S. K.; Chattopadhyay, B. Iron(II)-Based Metalloradical Activation: Switch from Traditional Click Chemistry to Denitrogenative Annulation. *Angew. Chem., Int. Ed.* **2019**. 58, 11439–11443.

(13) For select reviews, see: (a) Majumdar, K. C.; Mondal, S. Recent Developments in the Synthesis of Fused Sultams. *Chem. Rev.* **2011**, *111*, 7749–7773. For select examples, see: (b) Duan, J.; Chen, L.; Cherney, R. J.; Decicco, C. P.; Voss, M. E. Novel Cyclic Sulfonamide Derivatives as Metalloproteinase Inhibitors. WO9941246A1, **1999**. (c) Tozer, M. J.; Kalindjian, S. B.; Linney, I. D.; Steel, K. I. M.; Pether, M. J.; Cooke, T. Preparation of 1H-4(5)-Substituted Imidazoles as Histamine H3 Receptor Ligands. WO9905114A2, **1999**. (d) Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R. 1,2-Benzothiazine 1,1-Dioxide P2−P3 Peptide Mimetic Aldehyde Calpain I Inhibitors. *J. Med. Chem.* **2001**, *44*, 3488–3503. (e) Cherney, R. J.; Duan, J. J. W.; Voss, M. E.; Chen, L.; Wang, L.; Meyer, D. T.; Wasserman, Z. R.; Hardman, K. D.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Mandlekar, S.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. Design, Synthesis, and Evaluation of Benzothiadiazepine Hydroxamates as Selective Tumor Necrosis Factor-α Converting Enzyme Inhibitors. *J. Med. Chem.* **2003**, *46*, 1811–1823. (f) Baker, D. C.; Mayasundari, A.; Mao, J.; Johnson, S. C.; Yan, S. U.S. Patent 6,562,850 B1, **2003**. (g) Singh, S. K.; Reddy, P. G.; Rao, K. S.; Lohray, B. B.; Misra, P.; Rajjak, S. A.; Rao, Y. K.; Venkateswarlu, A. Polar Substitutions in the Benzenesulfonamide Ring of Celecoxib Afford a Potent 1,5-Diarylpyrazole Class of COX-2 Inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 499–504. (h) Valente, C.; Guedes, R. C.; Moreira, R.; Iley, J.; Gut, J.; Rosenthal, P. J. Dipeptide Vinyl Sultams: Synthesis via the Wittig–Horner Reaction and Activity Against Papain, Falcipain-2 and Plasmodium Falciparum. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4115–4119. (i) Zeng, W.; Chemler, S. R. Copper(II)-Catalyzed Enantioselective Intramolecular Carboamination of Alkenes. *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949. (j) Jiménez-Hopkins, M.; Hanson, P. R. An RCM Strategy to Stereodiverse δ-Sultam Scaffolds. *Org. Lett.* **2008**, *10*, 2223–2226.

(k) Rolfe, A.; Young, K.; Hanson, P. R. Domino Heck–Aza-Michael Reactions: A One-Pot, Sequential Three-Component Approach to 1,1-Dioxido-1,2-Benzisothiazoline-3-Acetic Acid. *Eur. J. Org. Chem.* **2008**, 5254-5262. (l) Rommel, M.; Fukuzumi, T.; Bode, J. W. Cyclic Ketimines as Superior Electrophiles for NHC-Catalyzed Homoenolate Additions with Broad Scope and Low Catalyst Loadings. *J. Am. Chem. Soc.* **2008**, *130*, 17266–17267. (m) Yu, C.-B.; Wang, D.-W.; Zhou, Y.-G. Highly Enantioselective Synthesis of Sultams via Pd-Catalyzed Hydrogenation. *J. Org. Chem.* **2009**, *74*, 5633–5635. (n) Ghosh, A. K.; Kulkarni, S.; Anderson, D. D.; Hong, L.; Baldridge, A.; Wang, Y.-F.; Chumanevich, A. A.; Kovalevsky, A. Y.; Tojo, Y.; Amano, M.; Koh, Y.; Tang, J.; Weber, I. T.; Mitsuya, H. Design, Synthesis, Protein−Ligand X-ray Structure, and Biological Evaluation of a Series of Novel Macrocyclic Human Immunodeficiency Virus-1 Protease Inhibitors to Combat Drug Resistance. *J. Med. Chem.* **2009**, *52*, 7689–7705. (o) Hanessian, S.; Larsson, A.; Fex, T.; Knecht, W.; Blomberg, N. Design and Synthesis of Macrocyclic Indoles Targeting Blood Coagulation Cascade Factor XIa. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6925–6928. (p) Swiderska, N.; Hawcutt, D.; Eaton, V.; Stockton, F.; Kumar, R.; Kneen, R.; Appleton, R. Sulthiame in Refractory Paediatric Epilepsies: An Experience of an 'Old' Antiepileptic Drug in a Tertiary Paediatric Neurology Unit. *Seizure* **2011**, *20*, 805–808. (q) Bodil Van Niel, M.; Fauber, B.; Gaines, S.; Gobbi, A.; Rene, O.; Vesey, D.; Ward, S. Aryl Sultam Derivatives as RORc Modulators and Their Preparation. WO2014009447A1, **2014**. (r) Aldrich, L. N.; Kuo, S.-Y.; Castoreno, A. B.; Goel, G.; Kuballa, P.; Rees, M. G.; Seashore-Ludlow, B. A.; Cheah, J. H.; Latorre, I. J.; Schreiber, S. L.; Shamji, A. F.; Xavier, R. J. Discovery of a Small-Molecule Probe for V-ATPase Function. *J. Am. Chem. Soc.* **2015**, *137*, 5563–5568. (s) Osborne, C. A.; Endean, T. B. D.; Jarvo, E. R. Silver-Catalyzed Enantioselective Propargylation Reactions of N-Sulfonylketimines. *Org. Lett.* **2015**, *17*, 5340–5343. (t) Shan, W.; Balog, A.; Nation, A.; Zhu, X.; Chen, J.; Cvijic, M. E.; Geng, J.; Rizzo, C. A.; Spires, T.; Attar, R. M.; Obermeier, M.; Traeger, S.; Dai, J.; Zhang, Y.; Galella, M.; Trainor, G.; Vite, G. D.; Gavai, A. V. [2.2.1]-Bicyclic Sultams as Potent Androgen Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5707–5711. (u) Kiran, I. N. C.; Reddy, R. S.; Lagishetti, C.; Xu, H.; Wang, Z.; He, Y. Selective Aza Diels–Alder and Domino [4+2]/[2+2] Cycloaddition Reactions of Arynes with N-Sulfonyl Ketimines. *J. Org. Chem.* **2017**, *82*, 1823–1832. (v) Khalifa, A.; Evans, P. The Titanium-Mediated Double Reductive Cleavage of Cyclic Sulfonamides for the Synthesis of Aryl Pyrrolidines. *J. Org. Chem.* **2019**, *84*, 2969–2975.

(14) For select reviews, see: (a) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247–9301. (b) Alderson, J. M.; Corbin, J. R.; Schomaker, J. M. Tunable, Chemo- and Site-Selective Nitrene Transfer Reactions through the Rational Design of Silver(I) Catalysts. *Acc. Chem. Res.* **2017**, *50*, 2147–2158. (c) Collet, F.; Lescot, C.; Dauban, P. Catalytic C–H Amination: the Stereoselectivity Issue. *Chem. Soc. Rev.* **2011**, *40*, 1926–1936.

(15) For select examples of non-asymmetric intramolecular C–H amination, see: (a) Huard, K.; Lebel, H. N-Tosyloxycarbamates as Reagents in Rhodium-Catalyzed C–H Amination Reactions. *Chem. - Eur. J.* **2008**, *14*, 6222–6230. (b) Hennessy, E. T.; Betley, T. A. Complex N-Heterocycle Synthesis via Iron-Catalyzed, Direct C–H Bond Amination. *Science* **2013**, *340*, 591–595. (c) Alderson, J. M.; Phelps, A. M.; Scamp, R. J.; Dolan, N. S.; Schomaker, J. M. Ligand-Controlled, Tunable Silver-Catalyzed C–H Amination. *J. Am. Chem. Soc.* **2014**, *136*, 16720–16723. (d) Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. Selective Formation of γ-Lactams via C–H Amidation Enabled by Tailored Iridium Catalysts. *Science* **2018**, *359*, 1016–1021. (e) Azek, E.; Khalifa, M.; Bartholoméüs, J.; Ernzerhof, M.; Lebel, H. Rhodium(II)-Catalyzed C−H Aminations using N-Mesyloxycarbamates: Reaction Pathway and By-Product Formation. *Chem. Sci.* **2019**, *10*, 718–729. (f) Baek, Y.; Betley, T. A. Catalytic C–H Amination Mediated by Dipyrrin Cobalt Imidos. *J. Am. Chem. Soc.* **2019**, *141*, 7797–7806. For metal-free C(sp^3)−H radical amination, see: (g) Evoniuk, C. J.; Gomes, G. d. P.; Hill, S. P.; Fujita, S.; Hanson, K.; Alabugin, I. V. Coupling N–H Deprotonation, C–H Activation, and Oxidation: Metal-Free C(sp^3)–H Aminations with Unprotected Anilines. *J. Am. Chem. Soc.* **2017**, *139*, 16210–16221. (h) Bafaluy, D.; Muñoz-Molina, J. M.; Funes-Ardoiz, I.; Herold, S.; de Aguirre, A. J.; Zhang, H.; Maseras, F.; Belderrain, T. R.; Pérez, P. J.; Muñiz, K. Copper-Catalyzed N−F Bond Activation for Uniform Intramolecular C−H Amination Yielding Pyrrolidines and Piperidines. *Angew. Chem., Int. Ed.* **2019**, *58*, 8912–8916.

(16) For select examples of intramolecular asymmetric C–H amination, see: (a) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. Highly Diastereo- and Enantioselective Intramolecular Amidation of Saturated C–H Bonds Catalyzed by Ruthenium Porphyrins. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465–3468. (b) Milczek, E.; Boudet, N.; Blakey, S. Enantioselective C–H Amination Using Cationic Ruthenium(II)–Pybox Catalysts. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825–6828. (c) Wang, H.; Park, Y.; Bai, Z.; Chang, S.; He, G.; Chen, G. Iridium-Catalyzed Enantioselective C(sp^3)–H Amidation Controlled by Attractive Noncovalent Interactions. *J. Am. Chem. Soc.* **2019**, *141*, 7194–7201. (d) Zhou, Z.; Chen, S.; Qin, J.; Nie, X.; Zheng, X.; Harms, K.; Riedel, R.; Houk, K. N.; Meggers, E. Catalytic Enantioselective Intramolecular C(sp^3)−H Amination of 2-Azidoacetamides. *Angew. Chem., Int. Ed.* **2019**, *58*, 1088–1093. (e) Xing, Q.; Chan, C.-M.; Yeung, Y.-W.; Yu, W.-Y. Ruthenium(II)-Catalyzed Enantioselective γ-Lactams Formation by Intramolecular C–H Amidation of 1,4,2-Dioxazol-5-Ones. *J. Am. Chem. Soc.* **2019**, *141*, 3849–3853.

(17) For a recent example of intermolecular asymmetric C–H amination, see: Nasrallah, A.; Boquet, V.; Hecker, A.; Retailleau, P.; Darses, B.; Dauban, P. Catalytic Enantioselective Intermolecular Benzylic C(sp^3)−H Amination. *Angew. Chem., Int. Ed.* **2019**, *58*, 8192–8196.

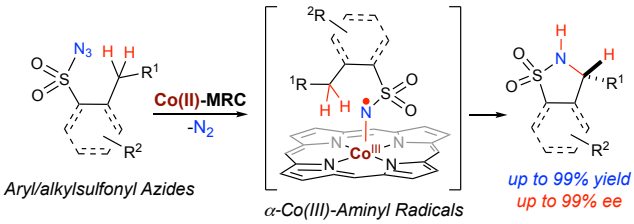
(18) For the first example of asymmetric cyclic sulfonamide formation via intramolecular C–H amination, see: (a) Fruit, C.; Müller, P. Intramolecular Asymmetric Amidations of Sulfonamides and Sulfamates Catalyzed by Chiral Dirhodium(II) Complexes. *Helv. Chim. Acta* **2004**, *87*, 1607–1615. For the only example of highly asymmetric benzofused cyclic sulfonamide formation via intramolecular C–H amination, see: (b) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. Enantioselective Intramolecular Benzylic C−H Bond Amination: Efficient Synthesis of Optically Active Benzosultams. *Angew. Chem., Int. Ed.* **2011**, *50*, 9884–9887.

(19) For select examples of synthesis and bioactivity studies on chiral fused-cyclic sulfonamides, see: (a) Samarakoon, T. B.; Loh, J. K.; Rolfe, A.; Le, L. S.; Yoon, S. Y.; Lushington, G. H.; Hanson, P. R., A Modular Reaction Pairing Approach to the Diversity-Oriented Synthesis of Fused- and Bridged-Polycyclic Sultams. *Org. Lett.* **2011**, *13*, 5148–5151. (b) Yin, X.; Zheng, Y.; Feng, X.; Jiang, K.; Wei, X.-Z.; Gao, N.; Chen, Y.-C. Asymmetric [5+3] Formal Cycloadditions with Cyclic Enones through Cascade Dienamine–Dienamine Catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 6245–6248. (c) Loh, J. K.; Asad, N.; Samarakoon, T. B.; Hanson, P. R. Modular, One-Pot, Sequential Aziridine Ring Opening–S_NAr Strategy to 7-, 10-, and 11-Membered Benzo-Fused Sultams. *J. Org. Chem.* **2015**, *80*, 9926–9941. Also see ref 13t.

(20) Brattesani, D. N.; Heathcock, C. H. Sulfenylation and Selenylation of Nitriles. *Tetrahedron Lett.* **1974**, *15*, 2279–2282.

(21) Grieco, P. A.; Gilman, S.; Nishizawa, M. A Facile One-Step Synthesis of Alkyl Aryl Selenides from Alcohols. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(22) Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. A Dual Metathesis Route to Oligomeric Sulfonamides. *Tetrahedron Lett.* **2002**, *43*, 917–921.


Co(II)-MRC
-N2
Aryl/alkylsulfonyl Azides
α-Co(III)-Aminyl Radicals
up to 99% yield
up to 99% ee