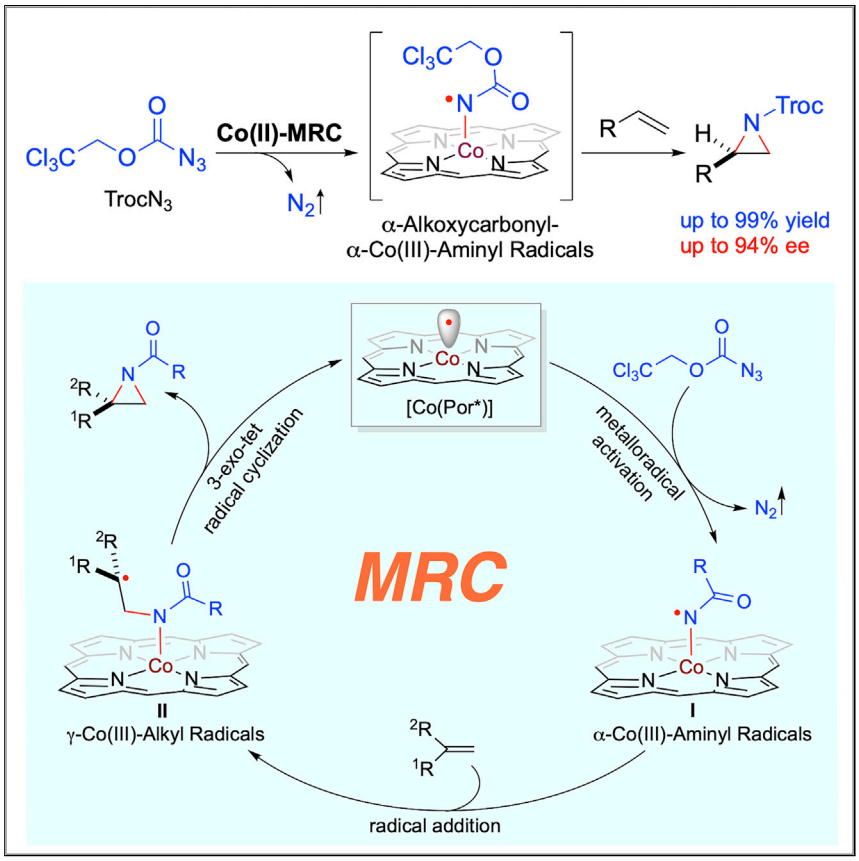
Chem

CellPress

Article

Metalloradical activation of carbonyl azides for enantioselective radical aziridination



A Co(II)-based system has been developed for enantioselective radical aziridination of alkenes using the carbonyl azide $TrocN_3$ as the nitrogen source. The catalytic system, which operates at room temperature under neutral and nonoxidative conditions, is applicable to both aromatic and electron-deficient olefins and enables the synthesis of *N*-carbonyl aziridines in high yields with excellent enantioselectivities. The enantioenriched *N*-carbonyl aziridines have been demonstrated as valuable intermediates for stereoselective organic synthesis. The Co(II)-catalyzed aziridination has been shown to proceed with stepwise radical mechanism.

Xavier Riart-Ferrer, Peng Sang, Jingran Tao, ..., Xin Cui, Lukasz Wojtas, X. Peter Zhang

peter.zhang@bc.edu

Highlights

Catalytic system for enantioselective aziridination of alkenes with $TrocN_3$

Highly enantioselective synthesis of chiral *N*-Troc-aziridines at room temperature

Systematic demonstration of chiral *N*-Troc-aziridines for stereoselective synthesis

Detailed mechanistic studies on elucidation of underlying stepwise radical pathway

Riart-Ferrer et al., Chem 7, 1120–1134
April 8, 2021 © 2021 Elsevier Inc.
https://doi.org/10.1016/j.chempr.2021.03.001

CellPress

Chem

Article

Metalloradical activation of carbonyl azides for enantioselective radical aziridination

Xavier Riart-Ferrer,[1,3] Peng Sang,[2,3] Jingran Tao,[2,3] Hao Xu,[1] Li-Mei Jin,[1] Hongjian Lu,[2] Xin Cui,[2] Lukasz Wojtas,[2] and X. Peter Zhang[1,4,*]

SUMMARY

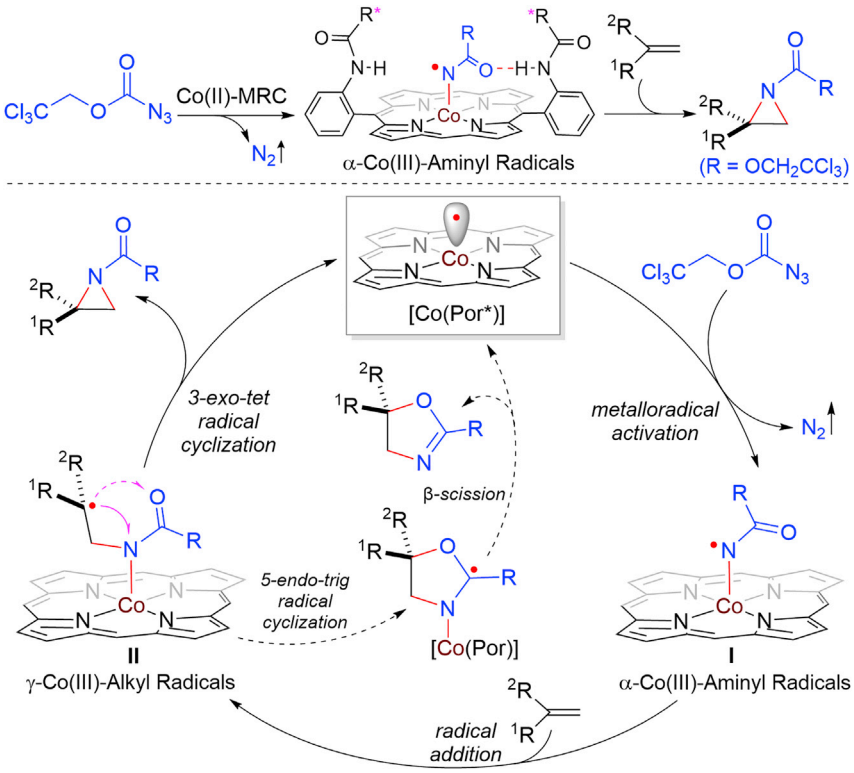
The carbonyl azide $TrocN_3$ (2,2,2-trichloroethoxycarbonyl azide) is a potent nitrogen radical precursor for radical olefin aziridination via Co(II)-based metalloradical catalysis (MRC). The cobalt(II) complex of D_2-symmetric chiral amidoporphyrin 3,5-Di^{t}Bu-QingPhyrin proves to be an efficient catalyst that can activate $TrocN_3$ at room temperature to aziridinate various styrene derivatives, providing chiral *N*-carbonyl aziridines in high yields with excellent enantioselectivities. The new Co(II)-based catalytic system can even enable asymmetric aziridination of electron-deficient alkenes, such as methyl and ethyl acrylates. In addition to facile removal of Troc group for generation of unprotected aziridines, the resulting *N*-Troc-aziridines can be effectively opened by different types of nucleophiles to afford a series of chiral amine derivatives with excellent stereospecificity. Several lines of computational and experimental evidence support the underlying stepwise radical mechanism for Co(II)-catalyzed olefin aziridination. This represents the first example of asymmetric intermolecular olefin aziridination that employs carbonyl azides as the nitrogen source.

INTRODUCTION

The development of selective radical reactions for applications in stereoselective organic synthesis has attracted growing research interest.[1] While radical reactions have a number of inherent synthetic advantages, such as fast reaction rate and functional group tolerance, their synthetic applications have been hampered by outstanding issues associated with control of reactivity and selectivity, especially in the context of enantioselectivity.[2] As stable metalloradicals, cobalt(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] have emerged as a family of open-shell transition metal catalysts for enantioselective radical transformations through catalytic generation of metal-supported organic radical intermediates via metalloradical catalysis (MRC).[3–5] Specifically, metalloradical catalysts [Co(D_2-Por*)] have shown to be particularly effective in activating organic azides to generate the corresponding α-Co(III)-aminyl radicals as key intermediates for catalytic radical aziridination of alkenes,[6] producing the smallest three-membered *N*-heterocycles with effective control of reactivity and enantioselectivity.[7,8] While previous reports involved the use of phosphoryl, sulfonyl, and aryl azides,[6] we were attracted to the possibility of using carbonyl azides, such as 2,2,2-trichloroethoxycarbonyl azide ($TrocN_3$), for radical olefin aziridination via Co(II)-MRC, especially its asymmetric variant by [Co(D_2-Por*)] (Scheme 1). Although [Co(TPP)] (TPP = 5,10,15,20-tetraphenylporphyrin) was previously shown to activate $TrocN_3$, it required elevated temperature and elongated reaction time, as well as the use of high catalyst loading.[9] We

The bigger picture

Organic azides have been increasingly employed as nitrogen sources for catalytic olefine aziridination due to their ease of preparation and generation of benign N_2 as the only byproduct. Among common organic azides, carbonyl azides have not been previously demonstrated as effective nitrogen sources for intermolecular olefin aziridination despite the synthetic utilities of N-carbonyl aziridines. As a new application of metalloradical catalysis, we have developed a catalytic system that can effectively employ the carbonyl azide $TrocN_3$ for highly asymmetric aziridination of alkenes at room temperature. The resulting enantioenriched *N*-Troc-aziridines have been shown as valuable chiral synthons for stereoselective synthesis of other chiral aziridines and various chiral amines. The Co(II)-based metalloradical system, which proceeds with distinctive stepwise radical mechanism, may provide a general method for asymmetric synthesis of chiral aziridines from alkenes with organic azides.



Scheme 1. Proposed mechanism for radical aziridination of alkenes with carbonyl azide $TrocN_3$ via Co(II)-MRC

reasoned that the metalloradical activation of $TrocN_3$ to generate α-2,2,2-trichloroethoxycarbonyl-α-Co(III)-aminyl radical intermediate **I** could be facilitated by [Co(D_2-Por*)] as a result of the putative H-bonding interaction between the carbonyl moiety in the azide and the amide unit of the catalyst (Scheme 1).[6d,6f] In view of the spin delocalization in the α-carbonylaminyl radical intermediate **I**, however, it was unclear whether it could function as effective nitrogen-centered radical to proceed radical addition to olefins for generation of γ-Co(III)-alkyl radical intermediate **II** (Scheme 1). Moreover, in order to form the expected aziridines, the resulting carbon-centered radical in intermediate **II** must undergo competitive *3-exo-tet* radical cyclization over *5-endo-trig* radical cyclization,[10] which would produce oxazolines after subsequent β-scission. More importantly, could the desired *3-exo-tet* radical cyclization proceed in an enantioselective fashion? We envisioned to address these and related issues of reactivity and selectivity through the judicious choice of metalloradical catalysts [Co(D_2-Por*)]. If successful, it would offer a new radical protocol for stereoselective synthesis of chiral *N*-carbonyl aziridines (Scheme 1), which have found synthetic and biological applications (see Figure S1).[11]

Organic azides have been increasingly employed as nitrogen sources for catalytic aziridination of alkenes due to their attractive attributes, such as ease of preparation and generation of benign N_2 as the only byproduct.[3g,11d,12] Among common organic azides, carbonyl azides have not been previously demonstrated as effective nitrogen sources for intermolecular olefin aziridination,[7b,13] despite the potential formation of useful aziridines bearing *N*-carbonyl functionality, which can also be easily deprotected to yield *N*–H aziridines.[11e] This underdevelopment is mainly attributed to the well-known challenges associated with the high lability of carbonyl

[1]Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467, USA

[2]Department of Chemistry, University of South Florida, Tampa, FL 33620, USA

[3]These authors contributed equally

[4]Lead contact

*Correspondence: peter.zhang@bc.edu

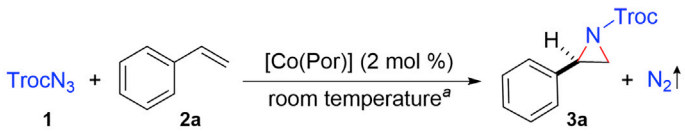
https://doi.org/10.1016/j.chempr.2021.03.001

azides toward thermal and photolytic rearrangements.[14] Yoon and coworkers recently reported the use of Ir-based catalysts as photosensitizers for activation of $TrocN_3$ with visible light to generate triplet free nitrenes that can be selectively trapped by various alkenes for non-asymmetric aziridination.[15] As a novel alternative to carbonyl azides, Lebel and coworkers successfully employed chiral *N*-tosyloxycarbamates as nitrogen sources for Rh_2-catalyzed diastereoselective aziridination of alkenes.[16] To the best of our knowledge, there has been no previous report on asymmetric catalytic system for olefin aziridination using $TrocN_3$ as nitrogen source. In comparison with other nitrene precursors, $TrocN_3$ offers several advantages: (1) straightforward synthesis from the commercially available 2,2,2-trichloroethoxy chloroformate in near quantitative yield; (2) generation of environmentally benign dinitrogen as the only byproduct; and (3) ease of deprotection form the resulting aziridine products to afford *N*–H aziridines. As a new application of Co(II)-MRC, we herein wish to report the development of the first asymmetric catalytic system that can effectively employ $TrocN_3$ for highly asymmetric aziridination of aromatic alkenes. Supported by D_2-symmetric chiral amidoporphyrin ligands, the Co(II)-based catalytic process allows for efficient synthesis of chiral *N*-Troc-aziridines with a high degree of enantiocontrol. In addition to the convenient access of chiral *N*–H-aziridines through mild deprotection, the utilities of the resulting chiral *N*-Troc-aziridines are further showcased by the synthesis of chiral amines through stereospecific ring-opening with nucleophiles of different nature without erosion of the original enantiopurity. We also describe our mechanistic studies on the proposed stepwise radical mechanism of the Co(II)-catalyzed aziridination.

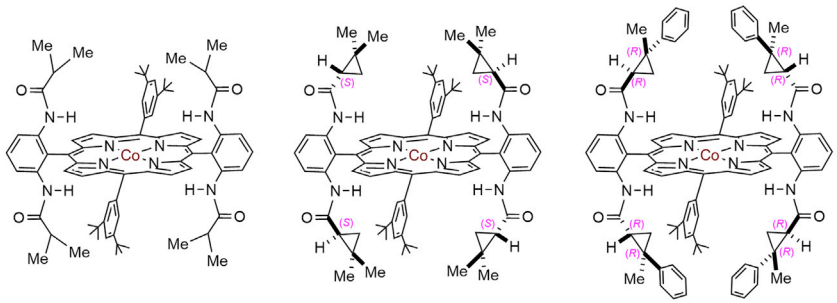
RESULTS AND DISCUSSION

Reaction optimization

Our efforts started with the use of styrene (**2a**) as the model substrate for asymmetric aziridination with $TrocN_3$ (**1**) by metalloradical catalysts [Co(Por)] (Figure 1). While [Co(TPP)] was ineffective (Figure 1; entry 1), the Co(II) complex of D_{2h}-symmetric achiral amidoporphyrin [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-IbuPhyrin)[6d] could catalyze the reaction even at room temperature to form the desired *N*-Troc-aziridine **3a** in a low but significant yield (Figure 1; entry 2), indicating ligand-accelerated catalysis as a result of the putative H-bonding interaction between the carbonyl moiety in the azide and the amide unit of the catalyst. The first-generation chiral metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-ChenPhyrin)[17] could give rise to significant asymmetric induction for the formation of chiral aziridine **3a** while slightly improving the yield (Figure 1; entry 3). Taking advantage of the modularity and tunability of the D_2-symmetric chiral amidoporphyrin ligand platform, we synthesized the second-generation metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-QingPhyrin) by replacing one of the methyl groups on the chiral amide units of [Co(**P2**)] with a phenyl group, resulting in a [Co(D_2-Por*)] complex bearing chiral amides with two contiguous stereogenic centers.[18] Gratifyingly, [Co(**P3**)] could further enhance both reactivity and enantioselectivity of the catalytic aziridination reaction, affording **3a** in 50% yield with 94% ee (Figure 1; entry 4). On the assumption that the presence of adventitious water might negatively affect the yield of the aziridine product, molecular sieves were employed as additives in the catalytic system. Indeed, the yield of aziridine **3a** was improved to 81% with preservation of the 94% ee (Figure 1; entry 5). It was further found that addition of anhydrous K_2CO_3 could lead to quantitative formation of the desired aziridine **3a** with the same excellent enantioselectivity (Figure 1; entry 6). While its exact role was difficult to ascertain, we speculated that anhydrous K_2CO_3 might, in addition to the removal of adventitious water-like molecular sieves, prevent Co(III)-intermediates from functioning as potential Lewis



entry	[Co(Por)]	solvent	additive	yield (%)[b]	ee (%)[c]
1	[Co(TPP)]	chlorobenzene	--	trace	0
2	[Co(**P1**)]	chlorobenzene	--	15	0
3	[Co(**P2**)]	chlorobenzene	--	22	76
4	[Co(**P3**)]	chlorobenzene	--	50	94
5	[Co(**P3**)]	chlorobenzene	M.S.[d]	81	94
6	**[Co(P3)]**	**chlorobenzene**	**K_2CO_3[e]**	**99**	**94**
7[f]	[Co(**P3**)]	chlorobenzene	K_2CO_3[e]	43	94
8	[Co(**P3**)]	trifluorotoluene	K_2CO_3[e]	84	94
9	[Co(**P3**)]	hexanes	K_2CO_3[e]	79	94
10	[Co(**P3**)]	dichloromethane	K_2CO_3[e]	trace	nd[g]
11	--	chlorobenzene	K_2CO_3[e]	--	--



[Co(**P1**)]
(**P1** = 3,5-Di^{t}Bu-IbuPhyrin)

[Co(**P2**)]
(**P2** = 3,5-Di^{t}Bu-ChenPhyrin)

[Co(**P3**)]
(**P3** = 3,5-Di^{t}Bu-QingPhyrin)

Figure 1. Enantioselective aziridination reaction of styrene with carbonyl azide $TrocN_3$ by [Co(Por)]

[a]Carried out at room temperature for 24 h with $TrocN_3$ (0.1 mmol) and styrene (0.3 mmol); [$TrocN_3$] = 0.10 M.

[b]Isolated yields.

[c]Enantiomeric excess determined by chiral HPLC.

[d]With 50 mg of 4 Å molecular sieves.

[e]With 0.5 mmol of anhydrous K_2CO_3.

[f]$TrocN_3$ (0.12 mmol) and styrene (0.1 mmol) were used.

[g]Not determined.

acids to promote aziridine isomerization.[19] Switching the ratio of **2a**:**1** from 3:1 to 1:1.2 resulted in decrease in the yield of **3a** without affecting the enantioselectivity (Figure 1; entry 7). Among different solvents tested (see Figure S2), chlorobenzene proved to be the choice of reaction medium, affording aziridine **3a** in high yield with excellent enantioselectivity at room temperature (Figure 1; entries 6–10). As expected, no reaction was observed in the absence of a catalyst (Figure 1; entry 11).

Substrate scope

Under the optimized reaction conditions, the [Co(**P3**)]/$TrocN_3$-based system was found to be effective for enantioselective aziridination of various styrene derivatives (Figure 2). Like styrene, the Co(II)-catalyzed aziridination was suitable for styrene derivatives bearing alkyl substituents at the *para*-, *meta*-, and *ortho*-positions, affording the desired aziridines **3b**–**3e** in moderate to high yields with excellent

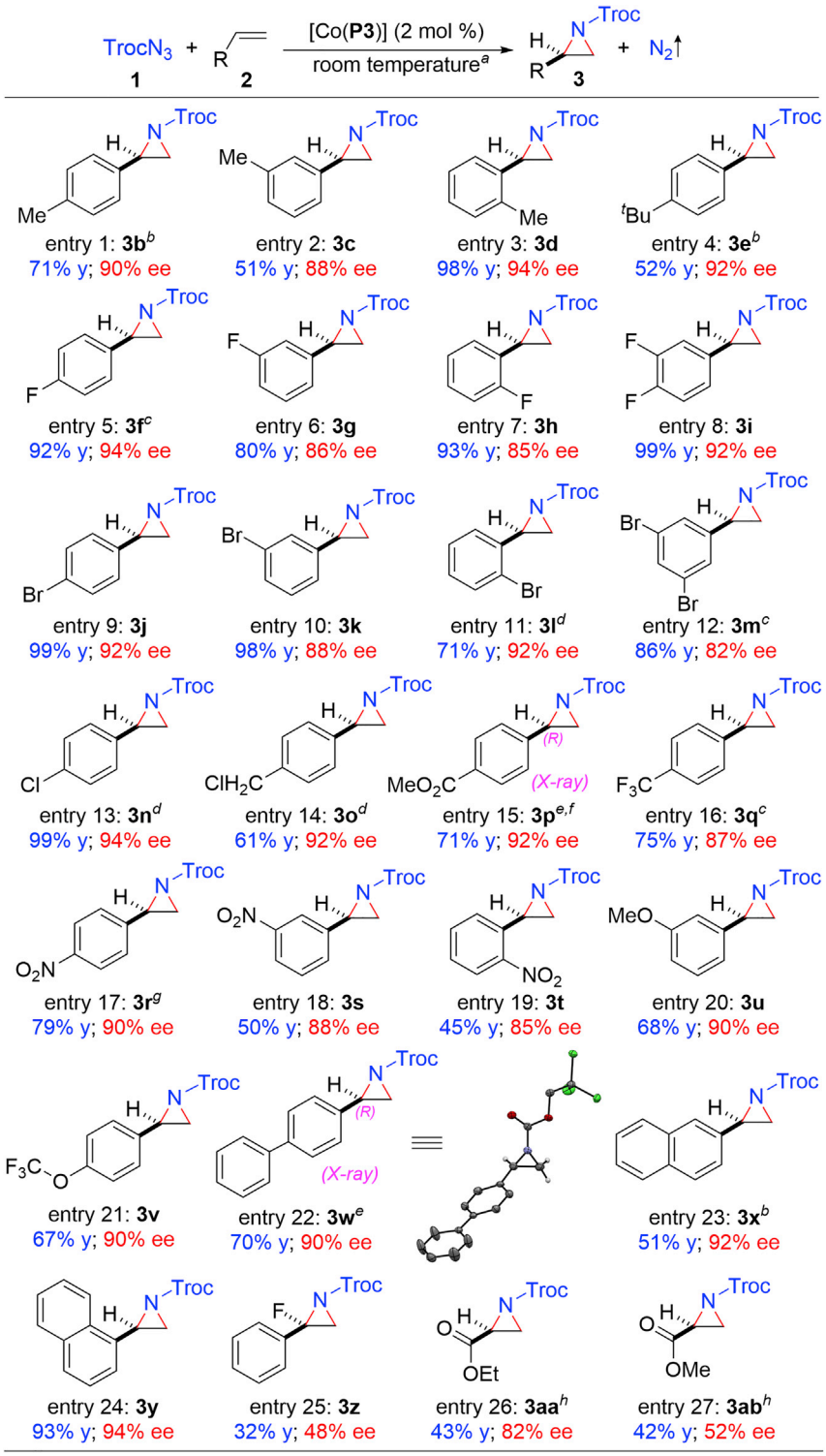


Figure 2. Co(II)-catalyzed enantioselective aziridination of styrene derivatives with carbonyl azide $TrocN_3$

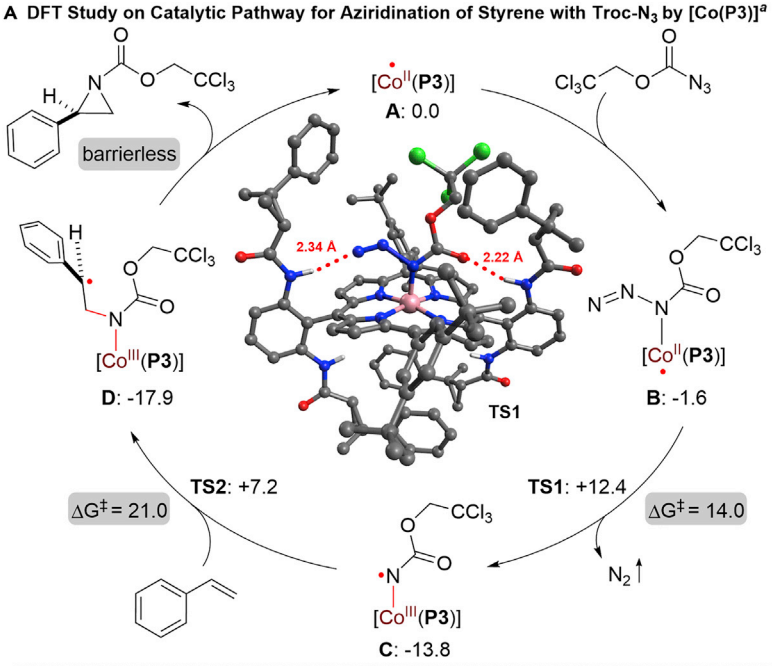
[a]Carried out with **1** (0.1 mmol), **2** (0.3 mmol), and K_2CO_3 (0.5 mmol) by [Co(**P3**)] (2 mol %) in chlorobenzene at room temperature for 24 h; [$TrocN_3$] = 0.10 M; Isolated yields; Enantiomeric excess determined by chiral HPLC.

[b]Used [Co(**P3**)] (5 mol %), **2** (0.5 mmol), and Cs_2CO_3 (0.5 mmol).

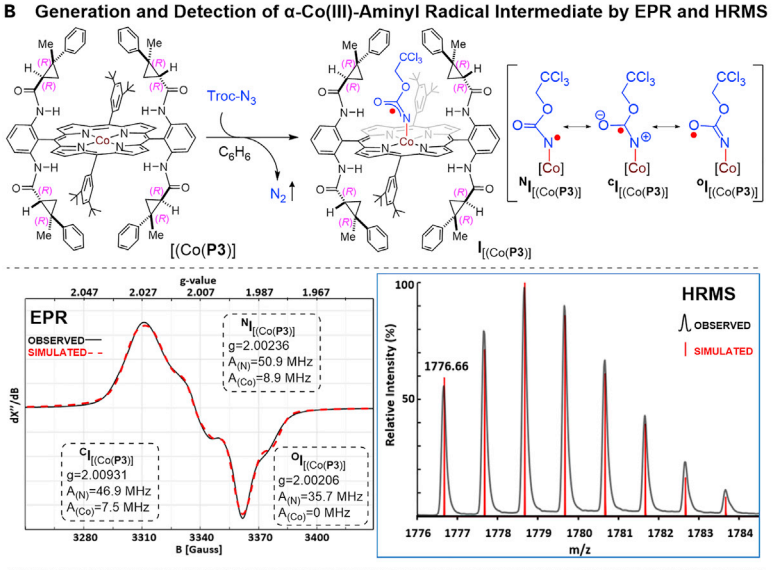
Figure 2. *Continued*
[c]At 0°C for 24 h.
[d]At 40°C for 24 h.
[e]Absolute configuration determined by anomalous dispersion effects in X-ray diffraction measurements on the crystal.
[f]51% Yield (815 mg); 92% ee when carried out on a gram scale with **1** (4.6 mmol), **2** (13.7 mmol), and K_2CO_3 (22.9 mmol) with [Co(**P3**)] (1 mol %).
[g]At –20°C for 48 h.
[h]Used [Co(**P3**)] (5 mol %) with addition of $Pd(OAc)_2$ (10 mol %) in the presence of 4 Å molecular sieves (50 mg) instead of K_2CO_3 at 40°C for 48 h.

enantioselectivities (Figure 2; entries 1–4). Fluorinated styrenes having different substitution patterns could be employed as effective substrates, providing the corresponding fluorinated aziridines **3f–3i** in high yields with excellent enantioselectivities (Figure 2; entries 5–8). Other halogenated aromatic olefins, such as brominated and chlorinated styrenes, could also be effectively aziridinated with $TrocN_3$, affording the halogenated aziridines **3j–3n** in high yields with excellent enantioselectivities (Figure 2; entries 9–13), which may be potentially transformed to other aziridine derivatives by cross-coupling and related reactions. Furthermore, the Co(II)-based system could tolerate functional groups as exemplified by productive formation of the desired aziridine **3o** and **3p** with high enantioselectivities (Figure 2; entries 14 and 15). To demonstrate the synthetic practicality, a gram-scale synthesis of aziridine **3p** was performed using 1 mol % of [Co(**P3**)] under otherwise the same conditions, affording the desired product with the same high enantioselectivity (92% ee) but in a relatively lower yield (from 71% to 51%). The reduction of the catalyst loading from 2 to 1 mol % is likely responsible for the lower yield. Additionally, styrene derivatives containing electron-withdrawing substituents, such as $–CF_3$ and $–NO_2$ groups at different positions, could serve as suitable substrates for the aziridination system, affording the corresponding three-membered *N*-heterocycles **3q–3t** in enantioenriched forms although in relatively lower yields (Figure 2; entries 16–19). Similarly, the Co(II)-catalyzed aziridination could be applied for styrene derivatives bearing electron-donating groups as demonstrated by the highly asymmetric formation of **3u** and **3v** albeit in lower yields (Figure 2; entries 20 and 21). In addition, the aziridination system by [Co(**P3**)] could be applied to extended aromatic olefins as shown by the construction of aziridines **3w–3y** in moderate to high yields with excellent enantioselectivities (Figure 2; entries 22–24). The absolute configurations of the newly generated stereogenic centers in both **3p** and **3w** were established as (*R*) by X-ray crystallography. Besides mono-substituted styrene derivatives, the catalytic system could be applicable to 1,1-disubstituted styrenes as exemplified by the productive formation of aziridine **3z** bearing a tertiary fluoride stereocenter from the reaction of α-fluorostyrene although in lower yield and enantioselectivity (Figure 2; entry 25). Assisted by a catalytic amount of $Pd(OAc)_2$,[6e] we found that the Co(II)-based metalloradical system could even aziridinate electron-deficient alkenes as shown for the successful reactions of ethyl and methyl acrylates to form the corresponding aziridines **3aa** and **3ab**, respectively, in moderate yields but with significant levels of enantiocontrol (Figure 2; entries 26–27). It is worth mentioning that electron-deficient alkenes are known to be challenging substrates for aziridination by existing catalytic systems involving electrophilic metallonitrenes as the key intermediate. When heteroaromatic olefins were used, however, it generated an unidentified mixture of products in low yields without observation of the corresponding aziridines. Catalyst [Co(**P3**)] were found to be ineffective for aziridination reactions of aliphatic and internal olefins with $TrocN_3$, as well as dienes. Evidently, a more effective catalyst needs to be developed for asymmetric aziridination with a broader scope of alkenes.

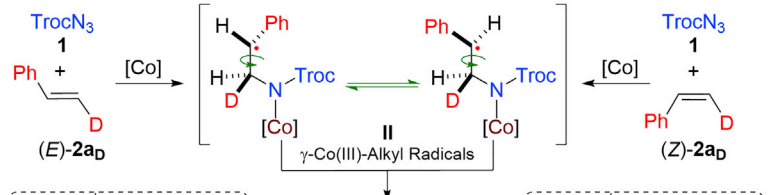
A DFT Study on Catalytic Pathway for Aziridination of Styrene with Troc-N_3 by [Co(P3)][a]



B Generation and Detection of α-Co(III)-Aminyl Radical Intermediate by EPR and HRMS



C Aziridination of *(E)*- or *(Z)*-β-Deuterostyrenes[b]



[Co]	(*Z*)-**3a**$_D$:(*E*)-**3a**$_D$
[Co(**P1**)]	20:80
[Co(**P2**)]	12:88
[Co(**P3**)]	01:99

[Co]	(*Z*)-**3a**$_D$:(*E*)-**3a**$_D$
[Co(**P1**)]	89:11
[Co(**P2**)]	94:06
[Co(**P3**)]	98:02

Scheme 2. Mechanistic studies for the [Co(P3)] catalyzed aziridination of styrene with $TrocN_3$

[a]All relative Gibbs free energies ($\Delta G°$) for intermediates and transition states, as well as activation energies ($\Delta G^{‡}$), are reported in kcal/mol.

[b]Carried out with **1** (0.1 mmol), $\mathbf{2a_D}$ (0.3 mmol), and K_2CO_3 (0.5 mmol) by [Co(Por)] (2 mol %) in chlorobenzene at 40 °C for 24 h; [$TrocN_3$] = 0.10 M; (*Z*)-$\mathbf{3a_D}$:(*E*)-$\mathbf{3a_D}$ ratio determined by ^{1}H-NMR and ^{2}H-NMR analysis of crude reaction mixture; see Supplemental information for details.

Mechanistic studies

Combined computational and experimental studies were performed for the proposed stepwise radical mechanism of the Co(II)-catalyzed aziridination (Scheme 1). First, density functional theory (DFT) calculations were carried out to study the catalytic pathway for aziridination reaction of styrene with $TrocN_3$ with the use of the actual catalyst [Co(**P3**)] (Scheme 2A).[20] The computational study indicates the existence of intermediate **B**, which is formed upon coordination of the internal nitrogen atom in $TrocN_3$ to the cobalt center of the catalyst. The formation of intermediate **B** is slightly exergonic by –1.6 kcal/mol due to additional H-bonding stabilization (see Schemes S6 and S7). Upon further activation, the coordinated azide undergoes dinitrogen elimination to generate α-Co(III)-aminyl radical **C**. The metalloradical activation step, which is exergonic by –12.2 kcal/mol, has a relative low activation energy (**TS1**: $\Delta G^{‡}$ = 14.0 kcal/mol). As shown in the middle of the catalytic cycle (see Schemes S6 and S7), the optimized **TS1** structure reveals strong double H-bond interactions (N–H—N: 2.34 Å; N–H—O: 2.22 Å) between [Co(**P3**)] and $TrocN_3$, as well as the strengthening of Co–N bonding interaction (as indicated by the decrease of bond distance from 2.10 to 1.90 Å). According to the DFT calculation, the subsequent radical addition of radical intermediate **C** to styrene is associated with a relatively high but accessible activation barrier (**TS2**: $\Delta G^{‡}$ = 21.0 kcal/mol), leading to the formation of γ-Co(III)-alkyl radical intermediate **D** (Scheme 2A). The final step of *3-exo-tet* cyclization via radical substitution, which is highly exergonic by –27.2 kcal/mol, is found to be almost barrierless, resulting in the formation of the three-membered aziridine **3a** and the regeneration of catalyst [Co(**P3**)]. For all computational details including cartesian coordinates of intermediates and transition states, see Data S1.

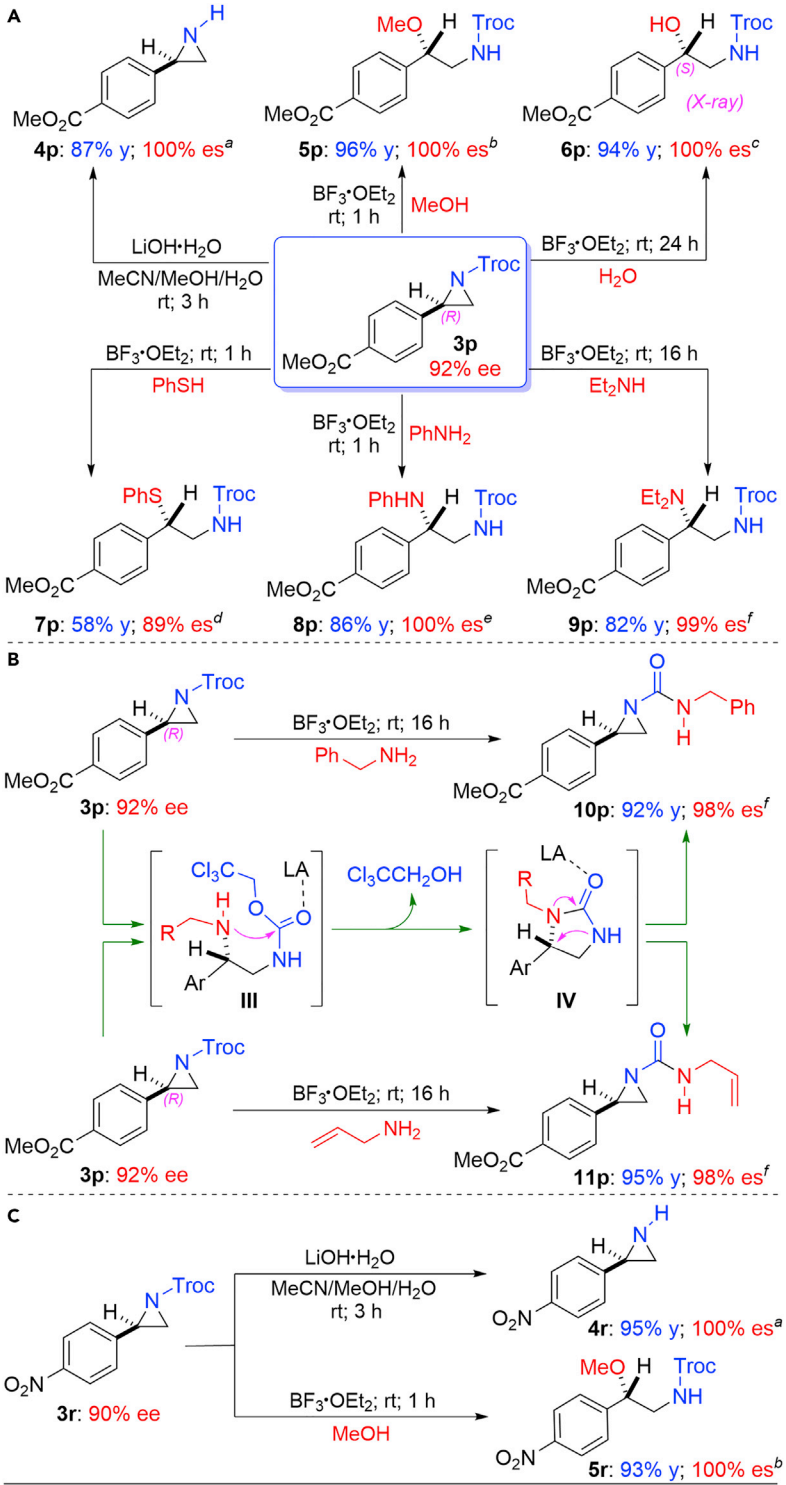
Second, in an effort to detect the α-Co(III)-aminyl radical intermediate **I** experimentally, the isotropic X-band electron paramagnetic resonance (EPR) spectrum was recorded at room temperature for the reaction mixture of [Co(**P3**)] with $TrocN_3$ (**1**) in benzene without alkene substrate (Scheme 2B). The spectrum displays salient signals akin to those characteristics of α-Co(III)-aminyl radicals (Scheme 2B).[8,21] The observed isotropic g value of 2.00 is consistent with the formation of organic radical $I_{[Co(P3)]}$ upon spin translocation from the Co(II) to the N-atom during metalloradical activation of the azide. In consistence with the spin delocalization in the α-carbonylaminyl radical intermediate $I_{[Co(P3)]}$, the observed broad signals could be fittingly simulated by invoking its three resonance forms on the basis of hyperfine couplings by both ^{14}N (I = 1) and ^{59}Co (I = 7/2): 17% of N-centered radical $^{N}I_{[Co(P3)]}$ (g: 2.00236; $A_{(Co)}$: 8.9 MHz; $A_{(N)}$: 50.9 MHz), 78% of C-centered radical $^{C}I_{[Co(P3)]}$ (g: 2.00931; $A_{(Co)}$: 7.5 MHz; $A_{(N)}$: 46.9 MHz), and 5% of O-centered radical $^{O}I_{[Co(P3)]}$ (g: 2.00206; $A_{(Co)}$: 0 MHz; $A_{(N)}$: 35.7 MHz) (see the Supplemental information for details). Furthermore, the α-Co(III)-aminyl radical $I_{[Co(P3)]}$ from the reaction mixture of [Co(**P3**)] with azide **1** could be detected by high-resolution mass spectrometry (HRMS) with electrospray ionization (ESI) ionization (see the Supplemental information for details). The obtained spectrum (Scheme 2B) evidently exhibited a signal corresponding to $[I_{[Co(P3)]}]^+$ (*m/z* = 1,776.6666), which resulted from the neutral α-Co(III)-aminyl radical $I_{[Co(P3)]}$ by the loss of one electron. Both the exact mass and the isotope distribution pattern measured experimentally matched well with those calculated from the

formula of [(**P3**)Co($NCO_2CH_2CCl_3$)]$^+$. The successful detection of α-Co(III)-aminyl radical intermediate $I_{[Co(P3)]}$ by EPR and HRMS provided experimental evidence to support the first step of metalloradical activation in the proposed mechanism of radical aziridination (Scheme 1).

Finally, to probe the subsequent steps of radical addition and radical cyclization in the proposed mechanism (Scheme 1), both isotopomers of β-deuterostyrene (*E*)-**2a**$_D$ and (*Z*)-**2a**$_D$ were applied as substrates for Co(II)-catalyzed aziridination with $TrocN_3$ (**1**) (Scheme 2C). While a concerted mechanism associated with metallonitrene intermediates is usually stereospecific, a stepwise mechanism involving α-Co(III)-aminyl radical intermediates may lead to the formation of aziridines as a mixture of both diastereoisomers (*E*)-**3a**$_D$ and (*Z*)-**3a**$_D$ from either (*E*)-**2a**$_D$ or (*Z*)-**2a**$_D$ as a result of the β-C−C bond rotation in the resulting γ-Co(III)-alkyl radical intermediate **II** before cyclization (Scheme 2C; Schemes S1 and S2). As expected, the aziridination of (*E*)-**2a**$_D$ with azide **1** by the achiral catalyst [Co(**P1**)] produced an isotopomeric mixture of (*Z*)-**3a**$_D$ and (*E*)-**3a**$_D$ in a ratio of 20:80. Under the identical conditions, aziridination of (*Z*)-**2a**$_D$ yielded the isotopomeric mixture in a ratio of 89:11. The formation of isotopomeric mixture of aziridine **3a**$_D$ from isomerically pure **2a**$_D$ is clearly attributed to the rotation around the β-C−C bond in the γ-Co(III)-alkyl radical intermediate **II**. Interestingly, it was found that the degree of the bond rotation could be influenced by the environment of the supporting ligand. For example, when the two reactions were carried out under the same condition but using the chiral catalyst [Co(**P2**)], the isotopomeric ratio of (*Z*)-**3a**$_D$ and (*E*)-**3a**$_D$ changed from 20:80 to 12:88 for the reaction of (*E*)-**2a**$_D$ and from 89:11 to 94:06 for the reaction of (*Z*)-**2a**$_D$, indicating a lower degree of rotation in a more hindered ligand environment (Scheme 2C). Accordingly, when the optimized catalyst [Co(**P3**)], which has an even more confined ligand environment, was employed for the aziridination reactions of (*E*)-**2a**$_D$ and (*Z*)-**2a**$_D$, minimal isotopomeric distributions were observed as a result of faster radical cyclization than the β-C–C bond rotation, leading to a stereospecific process (Scheme 2C). This high stereospecificity for β-deuterostyrenes, together with the high enantioselectivity observed for styrene (Figure 1, entry 6), implies that [Co(**P3**)]-catalyzed olefin aziridination with $TrocN_3$ involves radical addition as the enantiodetermining step, followed by a stereoretentive radical cyclization. As anticipated for a radical process, it was found that the catalytic aziridination process could be significantly inhibited when a large excess of TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl) was added. Together with the detection of the α-Co(III)-aminyl radical intermediate **I** by EPR and HRMS, these results fully corroborate the proposed stepwise radical mechanism for the Co(II)-based metalloradical aziridination (Scheme 1).

Synthetic applications

For access to aziridine derivatives with various *N*-substituents for different applications, it would be desirable that the aziridine products from a catalytic aziridination process could be effectively converted to the corresponding *N*–H aziridines through simple deprotection without opening the three-membered ring structures.[11e,22] In contrast to aziridines with *N*-protecting groups that require harsh conditions for deprotection,[23] *N*-carboalkoxy aziridines have been known to proceed facile *N*-deprotection under mild conditions.[24] To showcase the synthetic utilities of the resulting chiral *N*-Troc-aziridines from the Co(II)-catalyzed process, it was demonstrated that enantioenriched *N*-Troc-aziridine (*R*)-**3p** could be readily converted to the corresponding *N*–H aziridine **4p** in 87% yield without erosion of its optical purity when treated with lithium hydroxide at room temperature (Scheme 3A). In addition to *N*-deprotection, chiral *N*-Troc-aziridines were shown to undergo facile ring-opening reactions at room temperature by a wide range of nucleophiles in the presence of



Scheme 3. Transformations of chiral *N*-Troc-aziridines

[a]Conditions as reported in the literature.[24]

[b]MeOH (0.10 M), BF_3•OEt_2 (10 mol %).

[c]H_2O (0.10 M), BF_3•OEt_2 (10 mol %).

[d]PhSH (0.10 M), BF_3•OEt_2 (10 mol %).

[e]$PhNH_2$ (0.10 M), BF_3•OEt_2 (10 mol %).

[f]CH_2Cl_2 (0.10 M), BF_3•OEt_2 (20 mol %), amines (20 equiv).

Lewis acids with preservation of the high enantiomeric purity (Scheme 3A). For instance, methanol could effectively open the three-membered ring in (*R*)-**3p** in the presence of boron trifluoride diethyl etherate, generating chiral β-amino ether **5p** in 96% yield without any racemization. Notably, even water could function as an effective nucleophile for ring-opening of (*R*)-**3p** under similar conditions, resulting in highly stereospecific formation of chiral β-amino alcohol **6p** in 94% yield. The absolute configuration of **6p** was established by X-ray crystallography as (*S*), indicating an S_N2-type mechanism of the ring-opening reaction. Sulfur-based nucleophiles could also be applied for the ring-opening process as exemplified by the reaction of (*R*)-**3p** with thiophenol, affording the chiral β-amino thioether **7p** in 58% yield with some loss of the original enantiopurity. The three-membered ring in chiral *N*-Troc-aziridines could be readily opened by nitrogen-based nucleophiles, including both aromatic and aliphatic amines at room temperature to provide valuable vicinal diamines.[25] For example, both aniline and diethylamine could effectively react with (*R*)-**3p** to afford chiral vicinal diamines **8p** and **9p**, respectively, in high yields with no erosion of the original enantiopurity. Interestingly, when primary aliphatic amines were employed as the nucleophiles, the reactions of *N*-Troc-aziridines were found to proceed further to generate aziridine-based chiral ureas, a formal process that transforms carbamates to ureas via amide bond formation (Scheme 3B).[26] As two examples, benzylamine and allylamine reacted readily with (*R*)-**3p** under the similar conditions to form aziridine-based chiral ureas **10p** and **11p**, respectively, in excellent yields without apparent racemization. Presumably due to the combined high nucleophilicity of the resulting secondary amines and good leaving ability of trichloroethyl group, the initial ring-opening products **III** of (*R*)-**3p** by the primary amines proceeded further to form intramolecular amide bonds in the presence of Lewis acids to generate imidazolidinones **IV**, which then underwent ring-contraction under Lewis acid catalysis[27] to yield the final products **10p** and **11p**. The *N*-deprotection and ring-opening reactions could proceed equally well with other chiral *N*-Troc-aziridines as exemplified by the stereospecific formations of *N*–H aziridine **4r** and β-amino ether **5r** from enantioenriched aziridine **3r** (Scheme 3C).

Conclusions

In summary, we have developed the first catalytic system that can employ the carbonyl azide $TrocN_3$ as the nitrogen source for asymmetric aziridination via Co(II)-based MRC. With the support of 3,5-Di^{t}Bu-QingPhyrin as the chiral ligand, the Co(II)-based aziridination system with $TrocN_3$, which proceeds with the underlying stepwise radical mechanism as evidenced by the combined computational and experimental studies, provides a fundamentally new methodology for stereoselective synthesis of chiral *N*-Troc-aziridines from styrene derivatives with varied steric and electronic properties in high yields with high enantioselectivities. Assisted by a catalytic amount of $Pd(OAc)_2$, this new [Co(3,5-Di^{t}Bu-QingPhyrin)]/$TrocN_3$-based system can further catalyze asymmetric aziridination of electron-deficient alkenes, such as methyl and ethyl acrylates, which are challenging substrates for the catalytic systems involving electrophilic metallonitrene intermediates. Among several salient features, the Co(II)-catalyzed radical aziridination can operate efficiently at room temperature and has good functional group tolerance. The resulting enantioenriched *N*-Troc-aziridines have been showcased as valuable chiral synthons for stereoselective synthesis of other chiral aziridines and various chiral amine derivatives. Through fine-tuning the environments of D_2-symmetric chiral amidoporphyrins as the supporting ligand, we hope to develop a more general Co(II)-based catalytic system for enantioselective radical aziridination of different alkenes with $TrocN_3$.

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 materials transfer agreement if there is potential for commercial application.

Data and code availability

The crystal structure data of compound (R)-**3p**, (R)-**3w**, and (S)-**6p** have been deposited in the Cambridge structural database under reference numbers CCDC: 2025803, 2025804, and 2025805, respectively.

Full experimental procedures are provided in the Supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2021.03.001.

ACKNOWLEDGMENTS

We are grateful for financial support by NIH (R01-GM102554) and, in part, by NSF (CHE-1900375).

AUTHOR CONTRIBUTIONS

X.R.-F., P.S., and J.T. conducted the experiments. J.T. initiated the project. P.S. advanced the project. X.R.F. completed the project. H.X. carried out the DFT calculations. L.-M.J., H.L., and X.C. assisted the project. L.W. performed the X-ray crystallography studies. X.P.Z. conceived the work and coordinated the project. X.R.-F., P.S., J.T., and X.P.Z. designed the experiments. X.R.-F. and X.P.Z. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: August 31, 2020
Revised: December 9, 2020
Accepted: February 28, 2021
Published: March 29, 2021

REFERENCES

1. For select books, see:Chatgilialoglu, C., and Studer, A. (2012). Encyclopedia of Radicals in Chemistry, Biology and Materials (John Wiley & Sons).Curran, D.P., Porter, N.A., and Giese, B. (2008). Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications (John Wiley & Sons).Zard, S.Z. (2003). Radical Reactions in Organic Synthesis (Oxford University Press), For recent reviews, see: Zard, S.Z. (2019). Radical alliances: solutions and opportunities for organic synthesis. Helv. Chim. Acta *102*, e1900134.Huang, H.M., Garduño-Castro, M.H., Morrill, C., and Procter, D.J. (2019). Catalytic cascade reactions by radical relay. Chem. Soc. Rev. *48*, 4626–4638.Studer, A., and Curran, D.P. (2016). Catalysis of radical reactions: a radical chemistry perspective. Angew. Chem. Int. Ed. Engl. *55*, 58–102.Brimioulle, R., Lenhart, D., Maturi, M.M., and Bach, T. (2015). Enantioselective catalysis of photochemical reactions. Angew. Chem. Int. Ed. Engl. *54*, 3872–3890.Prier, C.K., Rankic, D.A., and MacMillan, D.W.C. (2013). Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. Chem. Rev. *113*, 5322–5363.Narayanam, J.M.R., and Stephenson, C.R.J. (2011). Visible light photoredox catalysis: applications in organic synthesis. Chem. Soc. Rev. *40*, 102–113.Quiclet-Sire, B.Z., and Zard, S.Z. (2011). Fun with radicals: some new perspectives for organic synthesis. Pure Appl. Chem. *83*, 519–551.Zard, S.Z. (2008). Recent progress in the generation and use of nitrogen-centred radicals. Chem. Soc. Rev. *37*, 1603–1618.

2. For select examples on approaches to control radical reactivity and selectivity, see:Du, J., Skubi, K.L., Schultz, D.M., and Yoon, T.P. (2014). A dual-catalysis approach to enantioselective [2 + 2] photocycloadditions using visible light. Science *344*, 392–396.Huo, H., Shen, X., Wang, C., Zhang, L., Röse, P., Chen, L.A., Harms, K., Marsch, M., Hilt, G., and Meggers, E. (2014). Asymmetric photoredox transition-metal catalysis activated by visible light. Nature *515*, 100–103.Lin, J.S., Dong, X.Y., Li, T.T., Jiang, N.C., Tan, B., and Liu, X.Y. (2016). A dual-catalytic strategy to direct asymmetric radical Aminotrifluoromethylation of alkenes. J. Am. Chem. Soc. *138*, 9357–9360.Kainz, Q.M., Matier, C.D., Bartoszewicz, A., Zultanski, S.L., Peters, J.C., and Fu, G.C. (2016). Asymmetric copper-catalyzed C–N cross-couplings induced by visible light. Science *351*, 681–684.Zhang, W., Wang, F., McCann, S.D., Wang, D., Chen, P., Stahl, S.S., and Liu, G. (2016). Enantioselective cyanation of benzylic C–H Bonds Via copper-catalyzed radical relay. Science *353*, 1014–1018.Funken, N., Mühlhaus, F., and Gansäuer, A. (2016). General, highly selective synthesis of 1,3- and 1,4-Difunctionalized building blocks by regiodivergent epoxide opening. Angew. Chem. Int. Ed. Engl. *55*, 12030–12034.Brill, Z.G., Grover, H.K., and Maimone, T.J. (2016). Enantioselective synthesis of an ophiobolin sesterterpene via a programmed radical cascade. Science *352*, 1078–1082.Kern, N., Plesniak, M.P., McDouall, J.J.W., and Procter, D.J. (2017). Enantioselective cyclizations and cyclization cascades of samarium ketyl radicals. Nat. Chem. *9*, 1198–1204.Morrill, C., Jensen, C., Just-Baringo, X., Grogan, G., Turner, N.J., and Procter, D.J. (2018). Biocatalytic conversion of cyclic ketones bearing α-quaternary stereocenters into lactones in an enantioselective radical approach to medium-sized carbocycles. Angew. Chem. Int. Ed. Engl. *57*, 3692–3696.Huang, H.-M., McDouall, J.J.W., and Procter, D.J. (2019). SmI_2-catalysed cyclization cascades by radical relay. Nat. Catal. *2*, 211–218.Ye, L., Tian, Y., Meng, X., Gu, Q.-S., and Liu, X.-Y. (2020). Enantioselective copper(I)/chiral phosphoric acid catalyzed intramolecular amination of allylic and benzylic C−H bonds. Angew. Chem. Int. Ed. Engl. *59*, 1129–1133.Li, X.-T., Lv, L., Wang, T., Gu, Q.-S., Xu, G.-X., Li, Z.-L., Ye, L., Zhang, X., Cheng, G.-J., and Liu, X.-Y. (2020). Diastereo- and enantioselective catalytic radical oxysulfonylation of alkenes in β,γ-unsaturated ketoximes. Chem *6*, 1692–1706.Roos, C.B., Demaerel, J., Graff, D.E., and Knowles, R.R. (2020). Enantioselective hydroamination of alkenes with sulfonamides enabled by proton-coupled electron transfer. J. Am. Chem. Soc. *142*, 5974–5979.Perego, L.A., Bonilla, P., and Melchiorre, P. (2020). Photo-organocatalytic enantioselective radical cascade enabled by single-electron transfer activation of allenes. Adv. Synth. Catal. *362*, 302–307.Cheng, Y.-F., Liu, J.-R., Gu, Q.-S., Yu, Z.-L., Wang, J., Li, Z.-L., Bian, J.-Q., Wen, H.-T., Wang, X.-J., Hong, X., et al. (2020). Catalytic enantioselective desymmetrizing functionalization of alkyl radicals via Cu(I)/CPA cooperative catalysis. Nat. Catal. *3*, 401–410.

3. For select reviews and highlights on Co(II)-based MRC, see Huang et al.,[1e] and:Demarteau, J., Debuigne, A., and Detrembleur, C. (2019). Organocobalt complexes as sources of carbon-centered radicals for organic and polymer chemistries. Chem. Rev. *119*, 6906–6955.Singh, R., and Mukherjee, A. (2019). Metalloporphyrin catalyzed C–H amination. ACS Catal *9*, 3604–3617.Pellissier, H., and Clavier, H. (2014). Enantioselective cobalt-catalyzed transformations. Chem. Rev. *114*, 2775–2823.Lu, H., and Zhang, X.P. (2011). Catalytic C–H functionalization by metalloporphyrins: recent developments and future directions. Chem. Soc. Rev. *40*, 1899–1909.Che, C.M., Lo, V.K.-Y., Zhou, C.Y., and Huang, J.S. (2011). Selective functionalisation of saturated C–H bonds with metalloporphyrin catalysts. Chem. Soc. Rev. *40*, 1950–1975.Driver, T.G. (2010). Recent advances in transition metal-catalyzed N-atom transfer reactions of azides. Org. Biomol. Chem. *8*, 3831–3846.Fantauzzi, S., Caselli, A., and Gallo, E. (2009). Nitrene transfer reactions mediated by metallo-porphyrin complexes. Dalton Trans *28*, 5434–5443.Doyle, M.P. (2009). Exceptional selectivity in cyclopropanation reactions catalyzed by chiral cobalt(II)–porphyrin catalysts. Angew. Chem. Int. Ed. Engl. *48*, 850–852.

4. For select examples of Ti(III)-based radical processes, see:Nugent, W.A., and Rajanbabu, T.V. (1988). Transition-metal-centered radicals in organic synthesis. Titanium(III)-induced cyclization of epoxy olefins. J. Am. Chem. Soc. *110*, 8561–8562.Rajanbabu, T.V., and Nugent, W.A. (1994). Selective generation of free radicals from epoxides using a transition-metal radical. A powerful new tool for organic synthesis. J. Am. Chem. Soc. *116*, 986–997.Gansäuer, A., Rinker, B., Pierobon, M., Grimme, S., Gerenkamp, M., and Mück-Lichtenfeld, C. (2003). A radical tandem reaction with homolytic cleavage of a ti–O bond. Angew. Chem. Int. Ed. Engl. *42*, 3687–3690.Gansäuer, A., Fan, C.A., Keller, F., and Keil, J. (2007). Titanocene-catalyzed regiodivergent epoxide openings. J. Am. Chem. Soc. *129*, 3484–3485.Gansäuer, A., Fleckhaus, A., Lafont, M.A., Okkel, A., Kotsis, K., Anoop, A., and Neese, F. (2009). Catalysis via homolytic substitutions with C−O and Ti−O bonds: oxidative additions and reductive eliminations in single electron steps. J. Am. Chem. Soc. *131*, 16989–16999.Gansäuer, A., Hildebrandt, S., Michelmann, A., Dahmen, T., von Laufenberg, D., Kube, C., Fianu, G.D., and Flowers, R.A. (2015). Cationic titanocene(III) complexes for catalysis in single-electron steps. Angew. Chem. Int. Ed. Engl. *54*, 7003–7006.Gansäuer, A., Hildebrandt, S., Vogelsang, E., and Flowers, R.A. (2016). Tuning the redox properties of the titanocene(III)/(IV)-couple for atom-economical catalysis in single electron steps. Dalton Trans *45*, 448–452.Hao, W., Wu, X., Sun, J.Z., Siu, J.C., MacMillan, S.N., and Lin, S. (2017). Radical redox-relay catalysis: formal [3+2] cycloaddition of N-Acylaziridines and alkenes. J. Am. Chem. Soc. *139*, 12141–12144.Klare, S., Gordon, J.P., Gansäuer, A., Rajanbabu, T.V., and Nugent, W.A. (2019). The reaction of β,γ-epoxy alcohols with titanium(III) reagents. A proposed role for intramolecular hydrogen bonding. Tetrahedron *75*, 130662.McCallum, T., Wu, X., and Lin, S. (2019). Recent advances in titanium radical redox catalysis. J. Org. Chem. *84*, 14369–14380.Yao, C., Dahmen, T., Gansäuer, A., and Norton, J. (2019). Anti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis. Science *364*, 764–767.Ye, K.Y., McCallum, T., and Lin, S. (2019). Bimetallic radical redox-relay catalysis for the isomerization of epoxides to allylic alcohols. J. Am. Chem. Soc. *141*, 9548–9554.

5. For select examples of catalytic radical processes involving metalloradical intermediates, see:Smith, D.M., Pulling, M.E., and Norton, J.R. (2007). Tin-free and catalytic radical cyclizations. J. Am. Chem. Soc. *129*, 770–771.Estes, D.P., Norton, J.R., Jockusch, S., and Sattler, W. (2012). Mechanisms by which alkynes react with $CpCr(CO)_3H$. Application to radical cyclization. J. Am. Chem. Soc. *134*, 15512–15518.Li, G., Han, A., Pulling, M.E., Estes, D.P., and Norton, J.R. (2012). 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. *134*, 14662–14665.Kuo, J.L., Hartung, J., Han, A., and Norton, J.R. (2015). Direct generation of oxygen-stabilized radicals by H● transfer from transition metal hydrides. J. Am. Chem. Soc. *137*, 1036–1039.

6. For intermolecular alkene aziridination, see:Caselli, A., Gallo, E., Ragaini, F., Ricatto, F., Abbiati, G., and Cenini, S. (2006). Chiral porphyrin complexes of cobalt(II) and ruthenium(II) in catalytic cyclopropanation and amination reactions. Inorg. Chim. Acta *359*, 2924–2932.Gao, G.Y., Jones, J.E., Vyas, R., Harden, J.D., and Zhang, X.P. (2006). Cobalt-catalyzed aziridination with diphenylphosphoryl azide (DPPA): direct synthesis of N-phosphorus-substituted aziridines from alkenes. J. Org. Chem. *71*, 6655–6658.Jones, J.E., Ruppel, J.V., Gao, G.Y., Moore, T.M., and Zhang, X.P. (2008). Cobalt-catalyzed asymmetric olefin aziridination with diphenylphosphoryl azide. J. Org. Chem. *73*, 7260–7265.Ruppel, J.V., Jones, J.E., Huff, C.A., Kamble, R.M., Chen, Y., and Zhang, X.P. (2008). A highly effective cobalt catalyst for olefin aziridination with azides: hydrogen bonding guided catalyst design. Org. Lett. *10*, 1995–1998.Subbarayan, V., Ruppel, J.V., Zhu, S., Perman, J.A., and Zhang, X.P. (2009). Highly asymmetric cobalt-catalyzed aziridination of alkenes with Trichloroethoxysulfonyl azide ($TcesN_3$). Chem. Commun. (Camb) 2009, 4266–4268.Jin, L.M., Xu, X., Lu, H., Cui, X., Wojtas, L., and Zhang, X.P. (2013). Effective synthesis of chiral N-Fluoroaryl aziridines through enantioselective aziridination of alkenes with fluoroaryl azides. Angew. Chem. Int. Ed. Engl. *52*, 5309–5313.Tao, J., Jin, L.M., and Zhang, X.P. (2014). Synthesis of chiral N-phosphoryl aziridines through enantioselective aziridination of alkenes with phosphoryl azide via Co(II)-based metalloradical catalysis. Beilstein J. Org. Chem. *10*, 1282–1289.Subbarayan, V., Jin, L.M., Xin, C., and Zhang, X.P. (2015). Room temperature activation of aryloxysulfonyl azides by [Co(II)(TPP)] for selective radical aziridination of alkenes via metalloradical catalysis. Tetrahedron Lett *56*, 3431–3434.Fantauzzi, S., Gallo, E., Caselli, A., Piangiolino, C., Ragaini, F., and Cenini, S. (2007). The (porphyrin) ruthenium-catalyzed aziridination of olefins using aryl azides as nitrogen sources. Eur. J. Org. Chem. 6053–6059.Caselli, A., Gallo, E., Fantauzzi, S., Morlacchi, S., Ragaini, F., and Cenini, S. (2008). Allylic amination and aziridination of olefins by aryl azides catalyzed by CoII (tpp): a synthetic and mechanistic study. Eur. J. Inorg. Chem. 3009–3019.Zardi, P., Pozzoli, A., Ferretti, F., Manca, G., Mealli, C., and Gallo, E. (2015). A mechanistic investigation of the ruthenium porphyrin

catalysed aziridination of olefins by aryl azides. Dalton Trans *44*, 10479–10489.

7. For intramolecular alkene aziridination, see:Jiang, H., Lang, K., Lu, H., Wojtas, L., and Zhang, X.P. (2016). Intramolecular radical aziridination of allylic sulfamoyl azides by cobalt(II)-based metalloradical catalysis: effective construction of strained heterobicyclic structures. Angew. Chem. Int. Ed. Engl. *55*, 11604–11608.Jiang, H., Lang, K., Lu, H., Wojtas, L., and Zhang, X.P. (2017). Asymmetric radical Bicyclization of allyl azidoformates via cobalt(II)-based metalloradical catalysis. J. Am. Chem. Soc. *139*, 9164–9167.Alderson, J.M., Corbin, J.R., and Schomaker, J.M. (2017). Tunable, chemo- and site-selective nitrene transfer reactions through the rational design of silver(I) catalysts. Acc. Chem. Res. *50*, 2147–2158.Ju, M., Weatherly, C.D., Guzei, I.A., and Schomaker, J.M. (2017). Chemo- and enantioselective intramolecular silver-catalyzed aziridinations. Angew. Chem. Int. Ed. Engl. *56*, 9944–9948.Corbin, J.R., Ketelboeter, D.R., Fernández, I., and Schomaker, J.M. (2020). Biomimetic 2-imino-Nazarov cyclizations via Eneallene aziridination. J. Am. Chem. Soc. *142*, 5568–5573.

8. For radical mechanism of [Co(D2-Por*)]-catalyzed aziridination and related amination, see:Jiang et al.,[7b] and references therein.Hu, Y., Lang, K., Li, C., Gill, J.B., Kim, I., Lu, H., Fields, K.B., Marshall, M., Cheng, Q., Cui, X., et al. (2019). Enantioselective radical construction of 5-membered cyclic sulfonamides by metalloradical C–H amination. J. Am. Chem. Soc. *141*, 18160–18169.Goswami, M., Lyaskovskyy, V., Domingos, S.R., Buma, W.J., Woutersen, S., Troeppner, O., Ivanović-Burmazović, I., Lu, H., Cui, X., Zhang, X.P., et al. (2015). Characterization of porphyrin-Co(III)-'nitrene radical' species relevant in catalytic nitrene transfer reactions. J. Am. Chem. Soc. *137*, 5468–5479.

9. Lu, H., Subbarayan, V., Tao, J., and Zhang, X.P. (2010). Cobalt(II)-catalyzed intermolecular benzylic C−H amination with 2,2,2-trichloroethoxycarbonyl azide ($Troc N_3$). Organometallics *29*, 389–393.

10. Cui, X., Xu, X., Wojtas, L., Kim, M.M., and Zhang, X.P. (2012). Regioselective synthesis of multisubstituted furans via metalloradical cyclization of alkynes with α-diazocarbonyls: construction of functionalized α-oligofurans. J. Am. Chem. Soc. *134*, 19981–19984.

11. Watson, I.D.G., Yu, L., and Yudin, A.K. (2006). Advances in nitrogen transfer reactions involving aziridines. Acc. Chem. Res. *39*, 194–206.Pellissier, H. (2010). Recent developments in asymmetric aziridination. Tetrahedron *66*, 1509–1555.Jiang, H., and Zhang, X.P. (2012). Oxidation: C–N bond formation by oxidation (aziridines). In Comprehensive Chirality, E.M. Carreira and H. Yamamoto, eds. (Elsevier), pp. 168–182.Degennaro, L., Trinchera, P., and Luisi, R. (2014). Recent advances in the stereoselective synthesis of aziridines. Chem. Rev. *114*, 7881–7929.Jat, J.L., Paudyal, M.P., Gao, H., Xu, Q.L., Yousufuddin, M., Devarajan, D., Ess, D.H., Kürti, L., and Falck, J.R. (2014). Direct stereospecific synthesis of unprotected N–H and N–me aziridines from olefins. Science *343*, 61–65.

12. Bräse, S., Gil, C., Knepper, K., and Zimmermann, V. (2005). Organic azides: an exploding diversity of a unique class of compounds. Angew. Chem. Int. Ed. Engl. *44*, 5188–5240.Katsuki, T. (2005). Azide compounds: nitrogen sources for atom-efficient and ecologically benign nitrogen-atom-transfer reactions. Chem. Lett. *34*, 1304–1309.

13. For select examples on non-asymmetric intramolecular alkene aziridination with carbonyl azides, see:Rhouati, S., and Bernou, A. (1989). Cyclisation of azidoformates, formation of aziridines. J. Chem. Soc. Chem. Commun. 730–732.Bergmeier, S.C., and Stanchina, D.M. (1997). Synthesis of vicinal amino alcohols via a tandem acylnitrene aziridination−aziridine ring opening. J. Org. Chem. *62*, 4449–4456.Bergmeier, S.C., and Stanchina, D.M. (1999). Acylnitrene route to vicinal amino alcohols. Application to the synthesis of (−)-bestatin and analogues. J. Org. Chem. *64*, 2852–2859.Kan, C., Long, C.M., Paul, M., Ring, C.M., Tully, S.E., and Rojas, C.M. (2001). Photo amidoglycosylation of an Allal azidoformate. Synthesis of β-2-amido allopyranosides. Org. Lett. *3*, 381–384.Yoshimitsu, T., Ino, T., and Tanaka, T. (2008). Total synthesis of (−)-agelastatin. A. Org. Lett. *10*, 5457–5460.Chang, Y.J., Hsuan, Y.C., Lai, A.C.-Y., Han, Y.C., and Hou, D.R. (2016). Synthesis of α-C-galactosylceramide via diastereoselective aziridination: the new immunostimulant 4′-epi-C-glycoside of KRN7000. Org. Lett. *18*, 808–811.Zhang, Y., Dong, X., Wu, Y., Li, G., and Lu, H. (2018). Visible-light-induced intramolecular C(sp_2)-H amination and aziridination of azidoformates via a triplet nitrene pathway. Org. Lett. *20*, 4838–4842.

14. Curtius, T. (1890). Ueber Stickstoffwasserstoffsäure (Azoimid) N3H. Ber. Dtsch. Chem. Ges. *23*, 3023–3033.Smith, P.A. (1946). The Curtius reaction. Org. React. 337–449.

15. Scholz, S.O., Farney, E.P., Kim, S., Bates, D.M., and Yoon, T.P. (2016). Spin-selective generation of triplet nitrenes: olefin aziridination through visible-light photosensitization of azidoformates. Angew. Chem. Int. Ed. Engl. *55*, 2239–2242.

16. Lebel, H., Spitz, C., Leogane, O., Trudel, C., and Parmentier, M. (2011). Stereoselective rhodium-catalyzed amination of alkenes. Org. Lett. *13*, 5460–5463.Lebel, H., Parmentier, M., Leogane, O., Ross, K., and Spitz, C. (2012). Copper bis(oxazolines) as catalysts for stereoselective aziridination of styrenes with N-Tosyloxycarbamates. Tetrahedron *68*, 3396–3409.Azek, E., Spitz, C., Ernzerhof, M., and Lebel, H. (2020). A mechanistic study of the stereochemical outcomes of rhodium-catalysed styrene aziridinations. Adv. Synth. Catal. *362*, 384–397.Lebel, H., and Parmentier, M. (2010). Copper-catalyzed enantioselective aziridination of styrenes. Pure Appl. Chem. *82*, 1827–1833.Lebel, H., Huard, K., and Lectard, S. (2005). N-Tosyloxycarbamates as a source of metal nitrenes: rhodium-catalyzed C−H insertion and aziridination reactions. J. Am. Chem. Soc. *127*, 14198–14199.

17. Chen, Y., Fields, K.B., and Zhang, X.P. (2004). Bromoporphyrins as versatile synthons for modular construction of chiral porphyrins: cobalt-catalyzed highly enantioselective and diastereoselective cyclopropanation. J. Am. Chem. Soc. *126*, 14718–14719.

18. Xu, X., Lu, H., Ruppel, J.V., Cui, X., Lopez de Mesa, S., Wojtas, L., and Zhang, X.P. (2011). 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. *133*, 15292–15295.

19. Heine, H., and Proctor, Z. (1958). Notes - isomerization of N-p-Ethoxybenzolethylenimine. J. Org. Chem. *23*, 1554–1556.Nishimura, M., Minakata, S., Takahashi, T., Oderaotoshi, Y., and Komatsu, M. (2002). Asymmetric N1 unit transfer to olefins with a chiral nitridomanganese complex: novel stereoselective pathways to aziridines or oxazolines. J. Org. Chem. *67*, 2101–2110.Luppi, G., and Tomasini, C. (2003). A new entry to polyfunctionalized 4,5-trans disubstituted oxazolidin-2-ones from l-aspartic acid. ChemInform *34*, 0797–0800.

20. For previous DFT studies on Co(II)-catalyzed aziridination with sulfonyl and aryl azides using simplified model catalysts, see:Suarez, A.I., Jiang, H., Zhang, X.P., and de Bruin, B. (2011). The radical mechanism of cobalt(II) porphyrin-catalyzed olefin aziridination and the importance of cooperative H-bonding. Dalton Trans *40*, 5697–5705.Hopmann, K.H., and Ghosh, A. (2011). Mechanism of cobalt-porphyrin–catalyzed aziridination. ACS Catal *1*, 597–600.

21. Lyaskovskyy, V., Suarez, A.I.O., Lu, H., Jiang, H., Zhang, X.P., and de Bruin, B. (2011). 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. *133*, 12264–12273.

22. For select examples on the significance of N–H aziridines, see 11e and:Lowden, P.A.S. (2006). Aziridine natural products – discovery, biological activity and biosynthesis. In Aziridines and Epoxides in Organic Synthesis, A.K. Yudin, ed. (Wiley-VCH Press), pp. 399–442.Lu, Z., Zhang, Y., and Wulff, W.D. (2007). Direct access to N–H-aziridines from asymmetric catalytic aziridination with borate catalysts derived from vaulted binaphthol and vaulted biphenanthrol ligands. J. Am. Chem. Soc. *129*, 7185–7194.Ismail, F.M.D., Levitsky, D.O., and Dembitsky, V.M. (2009). Aziridine alkaloids as potential therapeutic agents. Eur. J. Med. Chem. *44*, 3373–3387.Thibodeaux, C.J., Chang, W.C., and Liu, H.W. (2012). Enzymatic chemistry of cyclopropane, epoxide, and aziridine biosynthesis. Chem. Rev. *112*, 1681–1709.

23. Alonso, D.A., and Andersson, P.G. (1998). Deprotection of sulfonyl aziridines. J. Org. Chem. *63*, 9455–9461.Greene, T.W., and Wutts, P.G. (2006). Protection for the Amino Group. In Greene's Protective Groups in Organic Synthesis (John Wiley & Sons), pp. 696–926.Ankner, T., and Hilmersson, G. (2009). Instantaneous deprotection of tosylamides and esters with SmI_2/amine/water. Org. Lett. *11*, 1865.

24. Lebel, H., Lectard, S., and Parmentier, M. (2007). Copper-catalyzed alkene aziridination with N-Tosyloxycarbamates. Org. Lett. *9*, 4797–4800.

25. Lucet, D., Le Gall, T., and Mioskowski, C. (1998). The chemistry of vicinal diamines. Angew. Chem. Int. Ed. Engl. *37*, 2580–2627.Saibabu Kotti, S.R.S., Timmons, C., and Li, G. (2006). Vicinal diamino functionalities as privileged structural elements in biologically active compounds and exploitation of their synthetic chemistry. Chem. Biol. Drug Des. *67*, 101–114.Wu, B., Parquette, J.R., and Rajanbabu, T.V. (2009). Regiodivergent ring opening of chiral aziridines. Science *326*, 1662.Wu, B., Gallucci, J.C., Parquette, J.R., and Rajanbabu, T.V. (2009). Enantioselective Desymmetrization of meso-aziridines with TMSN3 or TMSCN Catalyzed by Discrete Yttrium Complexes. Angew. Chem. Int. Ed. Engl. *48*, 1126–1129.Wu, B., Gallucci, J.C., Parquette, J.R., and Rajanbabu, T.V. (2014). Bimetallic catalysis in the highly enantioselective ring–opening reactions of aziridines. Chem. Sci. *5*, 1102–1117.

26. For select examples on the significance of chiral ureas, see:Breuzard, J.A.J., Christ-Tommasino, M.L., and Lemaire, M. (2005). Chiral ureas and Thioureas in asymmetric catalysis. In Chiral Diazaligands for Asymmetric Synthesis, M. Lemaire and P. Mangeney, eds. (Springer), pp. 231–270.Doyle, A.G., and Jacobsen, E.N. (2007). Small-molecule H-bond donors in asymmetric catalysis. Chem. Rev. *107*, 5713–5743.

27. Hill, J.E., Matlock, J.V., Lefebvre, Q., Cooper, K.G., and Clayden, J. (2018). Consecutive ring expansion and contraction for the synthesis of 1-aryl tetrahydroisoquinolines and Tetrahydrobenzazepines from readily available heterocyclic precursors. Angew. Chem. Int. Ed. Engl. *57*, 5788–5791.