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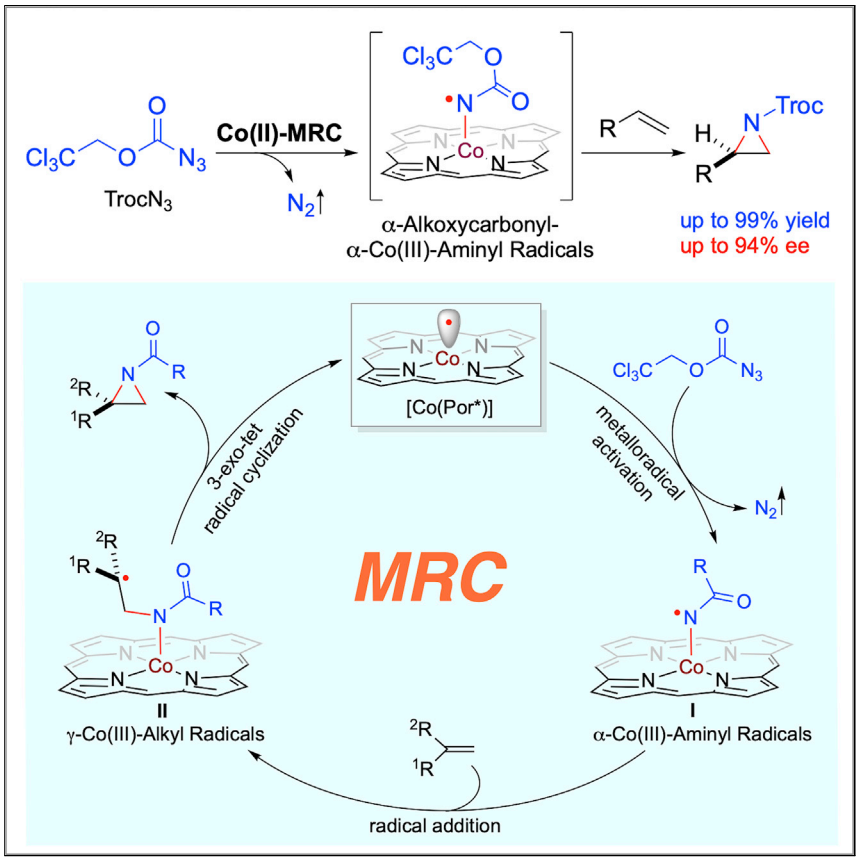
# Metalloradical activation of carbonyl azides for enantioselective radical aziridination




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

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## 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

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# Metalloradical activation of carbonyl azides for enantioselective radical aziridination

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## SUMMARY

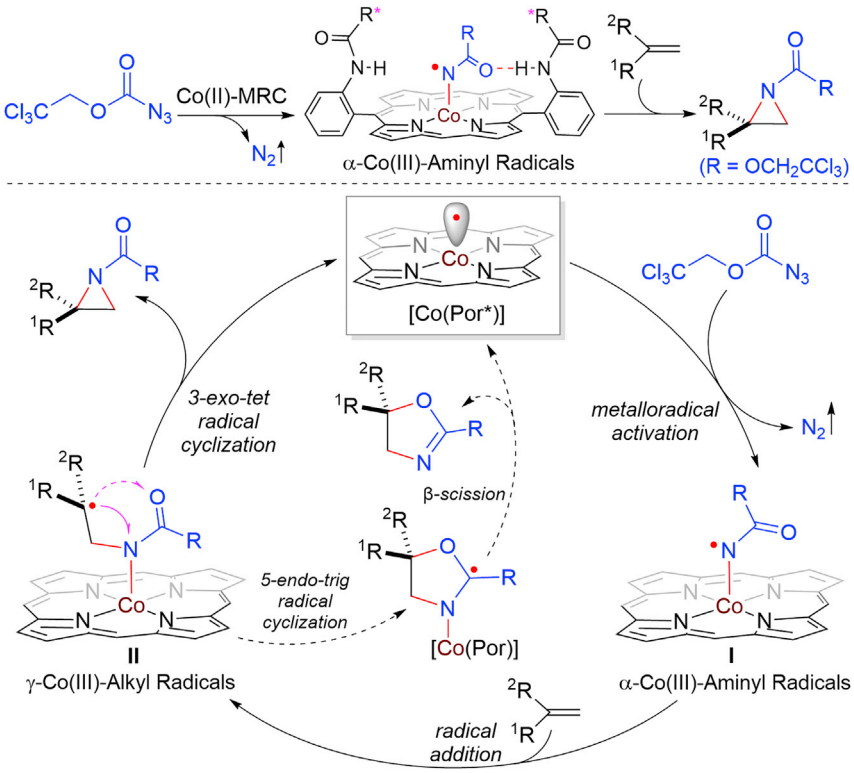
**The carbonyl azide $TrocN_3$ (2,2,2-trichloroethoxycarbonyl azide) is a potent nitrogen radical precursor for radical olefin aziridination via Co(II)-based metalloradical catalysis (MRC). The cobalt(II) complex of $D_2$-symmetric chiral amidoporphyrin 3,5-Di$^t$Bu-QingPhyrin proves to be an efficient 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

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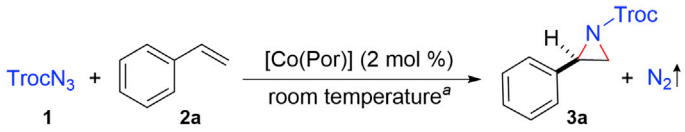
azides toward thermal and photolytic rearrangements.[14] Yoon and coworkers recently reported the use of Ir-based catalysts as photosensitizers for activation of $TrocN_3$ with visible light to generate triplet free nitrenes that can be selectively trapped by various alkenes for non-asymmetric aziridination.[15] 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.

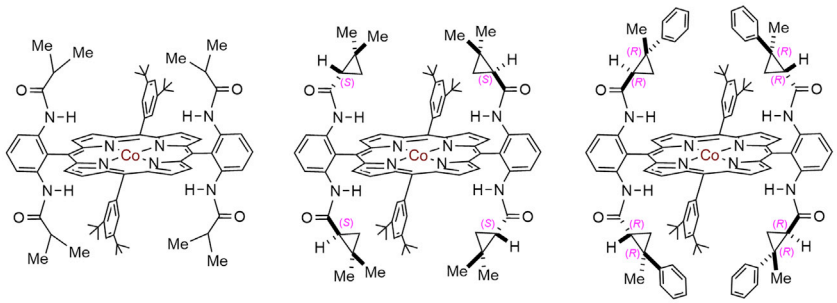
## RESULTS AND DISCUSSION

### 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

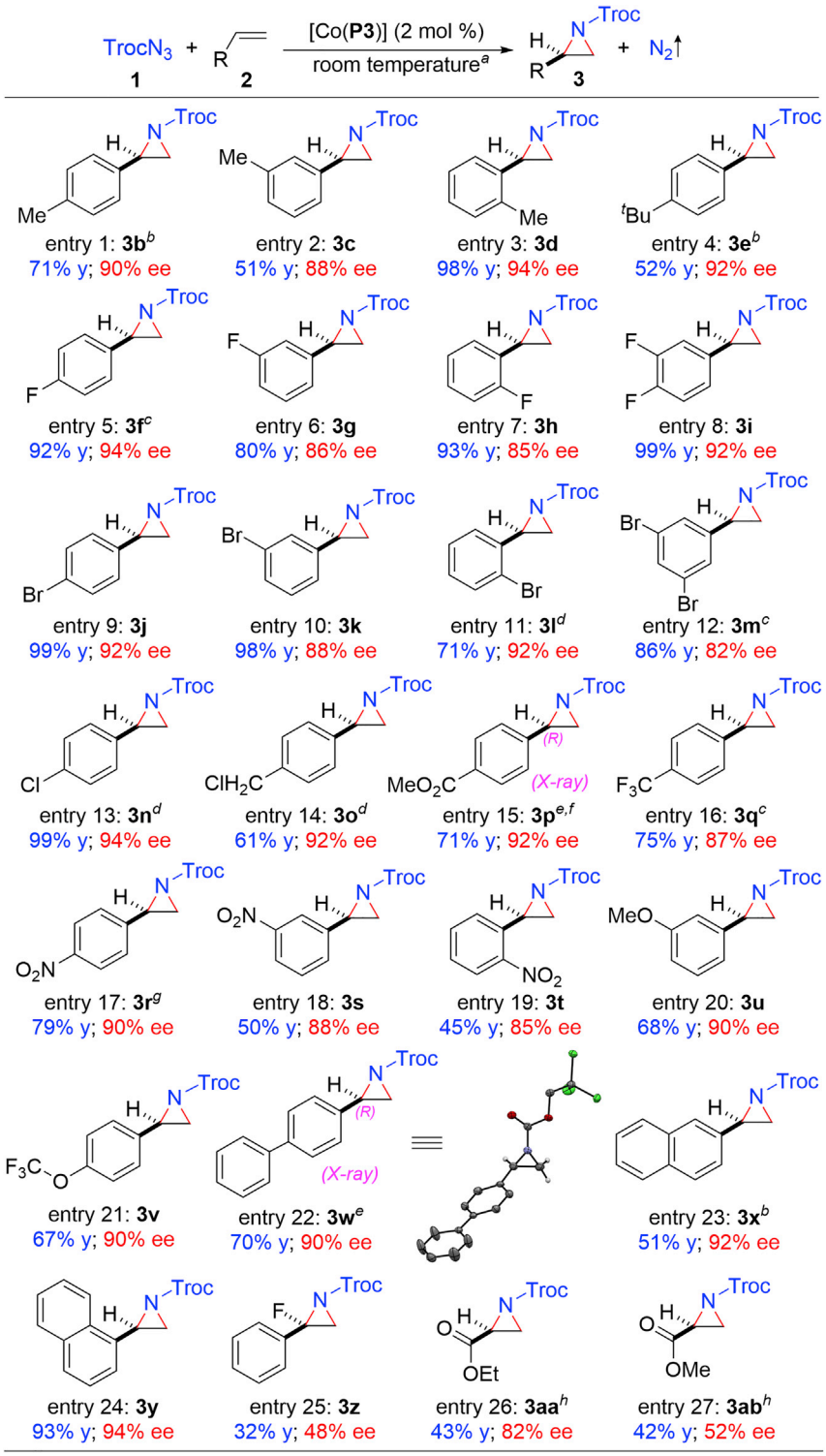



**Figure 2. Co(II)-catalyzed enantioselective aziridination of styrene derivatives with carbonyl azide $TrocN_3$**

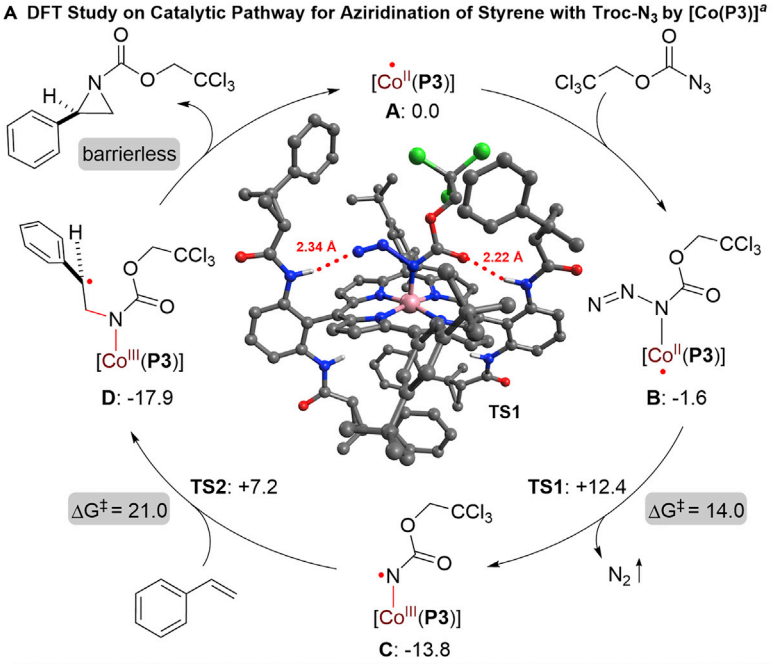
[a]Carried out with **1** (0.1 mmol), **2** (0.3 mmol), and $K_2CO_3$ (0.5 mmol) by [Co(**P3**)] (2 mol %) in chlorobenzene at room temperature for 24 h; [$TrocN_3$] = 0.10 M; Isolated yields; Enantiomeric excess determined by chiral HPLC.

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

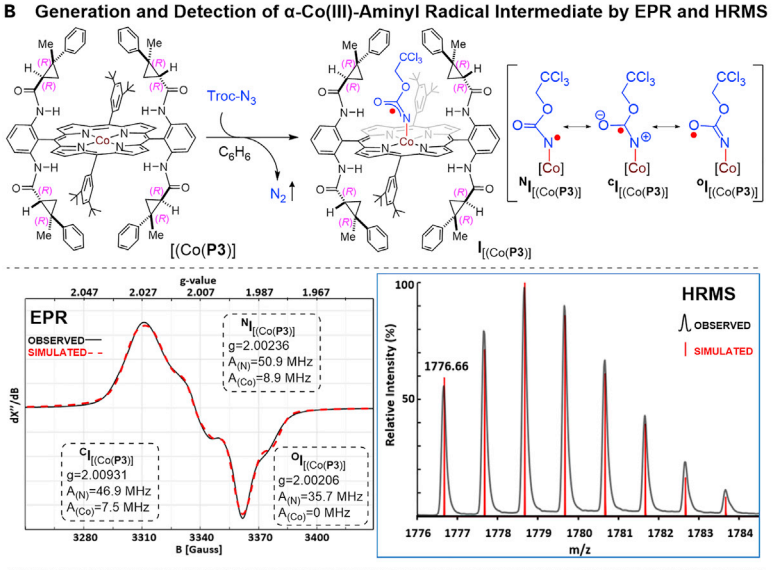
**Figure 2. *Continued***
[c]At 0°C for 24 h.
[d]At 40°C for 24 h.
[e]Absolute configuration determined by anomalous dispersion effects in X-ray diffraction measurements on the crystal.
[f]51% Yield (815 mg); 92% ee when carried out on a gram scale with **1** (4.6 mmol), **2** (13.7 mmol), and $K_2CO_3$ (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.

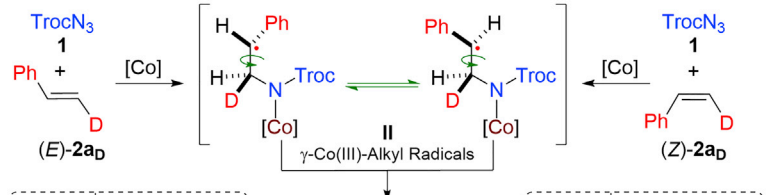
**A DFT Study on Catalytic Pathway for Aziridination of Styrene with Troc-$N_3$ by [Co(P3)]**[a]




**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.

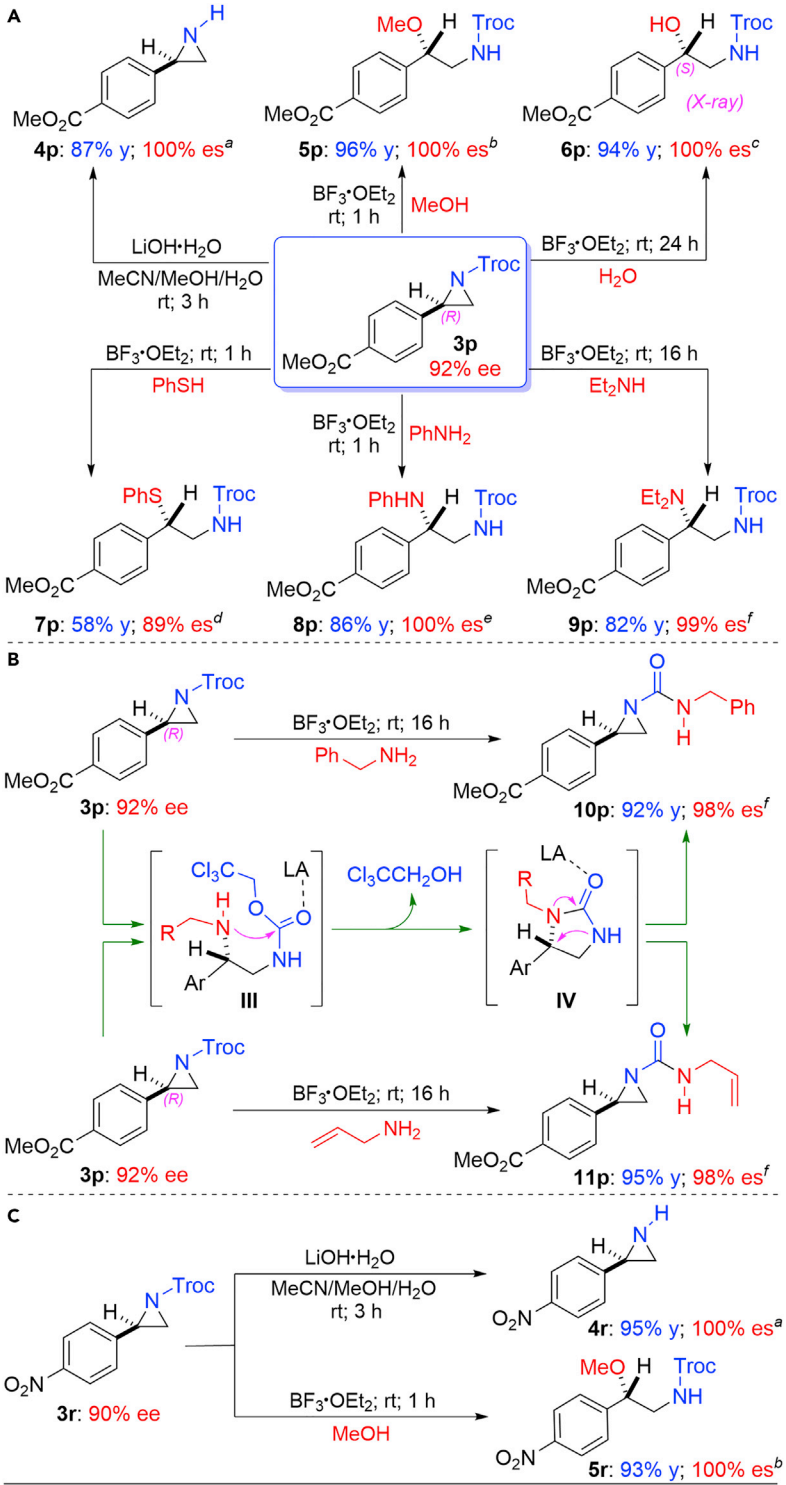
Second, in an effort to detect the α-Co(III)-aminyl radical intermediate **I** experimentally, the isotropic X-band electron paramagnetic resonance (EPR) spectrum was recorded at room temperature for the reaction mixture of [Co(**P3**)] with $TrocN_3$ (**1**) in benzene without alkene substrate (Scheme 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.

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## 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.

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