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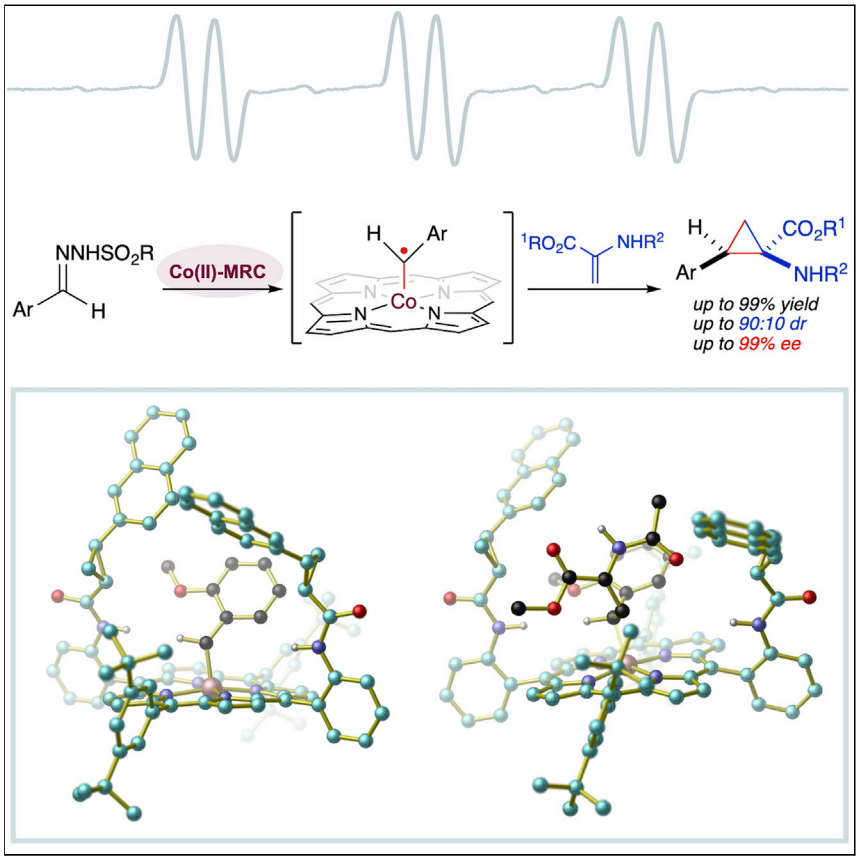
Asymmetric radical cyclopropanation of dehydroaminocarboxylates: Stereoselective synthesis of cyclopropyl α-amino acids



Cobalt(II)-based metalloradical catalysis (MRC) has been successfully applied for the development of a new catalytic radical process that is highly effective for asymmetric cyclopropanation of dehydroaminocarboxylates with *in situ*-generated α-aryldiazomethanes. Supported by an optimal D_2-symmetric chiral amidoporphyrin ligand, the Co(II)-based catalytic system is applicable to broad combinations of α-aryldiazomethanes and dehydroaminocarboxylates. In addition to high yields and excellent enantioselectivities, the Co(II)-catalyzed asymmetric cyclopropanation enables direct synthesis of α-amino-β-arylcyclopropanecarboxylates with (*Z*)-diastereoselectivity, which is different from uncatalyzed thermal reaction.

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Highlights

Asymmetric catalytic system for cyclopropanation of dehydroaminocarboxylates

Asymmetric synthesis of chiral cyclopropyl α-amino acids under mild conditions

Detailed mechanistic studies on elucidation of underlying stepwise radical pathway

Importance of attractive noncovalent interactions in catalyst development

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Asymmetric radical cyclopropanation of dehydroaminocarboxylates: Stereoselective synthesis of cyclopropyl α-amino acids

Wan-Chen Cindy Lee,[1] Duo-Sheng Wang,[1] Congzhe Zhang,[1] Jingjing Xie,[1] Bo Li,[1] and X. Peter Zhang[1,2,*]

SUMMARY

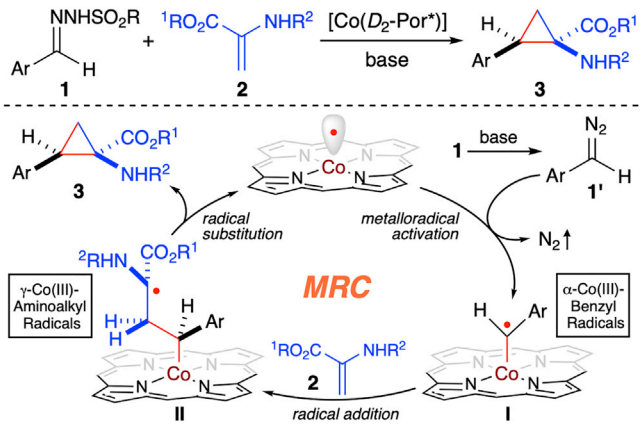
A catalytic radical process has been developed for asymmetric cyclopropanation of dehydroaminocarboxylates with *in situ*-generated α-aryldiazomethanes via Co(II)-based metalloradical catalysis (MRC). Through fine-tuning the environments of D_2-symmetric chiral amidoporphyrin platform as the supporting ligands, the Co(II)-metalloradical system can effectively activate various α-aryldiazomethanes to cyclopropanate different dehydroaminocarboxylates under mild conditions, enabling the stereoselective synthesis of chiral cyclopropyl α-amino acid derivatives. In addition to high yields and excellent enantioselectivities, the Co(II)-catalyzed asymmetric radical cyclopropanation exhibits (*Z*)-diastereoselectivity, which is the opposite of uncatalyzed thermal reaction. Combined computational and experimental studies support a stepwise radical mechanism for the Co(II)-catalyzed cyclopropanation reaction. The resulting enantioenriched (*Z*)-α-amino-β-arylcyclopropanecarboxylates, as showcased for the efficient synthesis of dipeptides, may serve as unique non-proteinogenic amino acid building blocks for the design and preparation of novel peptides with restricted conformations.

INTRODUCTION

Radical chemistry has been increasingly explored for the development of new synthetic tools in construction of organic molecules due to its unique reactivity and attractive characteristics, such as mild reaction condition and functional group tolerance.[1] However, controlling stereoselectivity, especially enantioselectivity, of radical reactions has remained a paramount challenge.[2] Among recent advances,[3] metalloradical catalysis (MRC) has emerged as a new approach to use metal-centered radicals to generate metal-stabilized organic radicals for achieving the control of reactivity and stereoselectivity in radical processes.[4–6] As stable 15e-metalloradicals, Co(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] exhibit unusual capability of homolytically activating different classes of diazo compounds to generate α-Co(III)-alkyl radicals.[7] These Co-supported C-centered radical intermediates are capable of radical addition to alkenes to deliver γ-Co(III)-alkyl radicals, which can undergo intramolecular radical substitution for catalytic formation of chiral cyclopropanes with control of diastereoselectivity and enantioselectivity.[8] Although monosubstituted alkenes, including styrene derivatives and α,β-unsaturated carbonyls, as well as aliphatic olefins, have been demonstrated as suitable substrates for Co(II)-based metalloradical system,[8] asymmetric radical cyclopropanation with 1,1-disubstituted alkenes remains rather underdeveloped. In particular, we were interested in exploring the potential application of Co(II)-based MRC for

The bigger picture

Chiral cyclopropyl α-amino acids represent a unique class of non-proteinogenic α-amino acids that have found wide applications in the design and synthesis of novel peptides with restricted conformations that are of biological importance. As a practical application of metalloradical catalysis (MRC), we have developed an asymmetric catalytic system that is highly effective for direct cyclopropanation of dehydroaminocarboxylates with *in situ*-generated α-aryldiazomethanes. The Co(II)-based catalytic system, which operates under mild conditions, enables high-yielding preparation of chiral cyclopropyl α-amino acids with excellent enantioselectivity and atypical (*Z*)-diastereoselectivity. Fundamentally, the underlying stepwise radical mechanism of Co(II)-catalyzed cyclopropanation has been elucidated by combined experimental and computational studies, revealing the importance of cooperative noncovalent interactions, such as H-bonding and π-stacking, in catalyst design and development.



Scheme 1. Proposed mechanism for radical cyclopropanation of dehydroaminocarboxylates via Co(II)-based metalloradical catalysis

asymmetric cyclopropanation of dehydroaminocarboxylates (Scheme 1), a class of 1,1-disubstituted alkenes that have been widely employed in catalytic asymmetric hydrogenation for synthesis of chiral α-amino acids.[9] Considering the unique steric and electronic properties of dehydroaminocarboxylates, their suitability as substrates for Co(II)-based radical cyclopropanation was unsettled and presented several potential challenges. In the specific case of using *in situ*-generated α-aryldiazomethanes **1′** as the radical precursor (also termed as "metalloradicophile"),[8i] it was unclear how the radical addition of the initially formed α-Co(III)-benzyl radical intermediate **I** with the 1,1-disubstituted alkene could be impacted by the steric hinderance associated with the two geminal substituents. Furthermore, during this first C–C bond forming step, differentiation of the two prochiral faces of the Co-bonded C-centered radical **I** for controlling enantioselectivity could be challenging in view of the similar sizes of the two geminal amino and ester groups in alkene **2**. For the same reasons, issues could also be encountered with the control of both reactivity and diastereoselectivity in the subsequent *3-exo-tet* radical cyclization of the resulting γ-Co(III)-aminoalkyl radicals **II** (Scheme 1). Besides the steric concerns, the second C–C bond forming process might also experience an adverse electronic effect in the light of higher stability of the tertiary radical intermediate **II** as a result of captodative effect from the ester group and amino group.[10] Additional uncertainty might arise from potential H-bonding interactions between the amino/ester groups and the amide units on the amidoporphyrin ligand. We hoped to address these and related issues through the identification of a D_2-symmetric chiral amidoporphyrin ligand with proper electronic, steric, and chiral environments that could govern the course of the Co(II)-based radical process as proposed. If successful, it would lead to the development of the first asymmetric catalytic system that catalyzes direct cyclopropanation of dehydroaminocarboxylates with diazo compounds for stereoselective synthesis of chiral cyclopropyl α-amino acid derivatives **3**. Chiral cyclopropyl α-amino acid derivatives represent a unique class of non-proteinogenic α-amino acids that have found interesting applications in the design and synthesis of novel peptides with restricted conformations (Figures S1 and S2).[11,12] Although several synthetic methods have been previously reported,[11,12] it is warranted to develop new catalytic systems for asymmetric synthesis of chiral cyclopropyl α-amino acid derivatives that are generally applicable and highly enantioselective.

Metal-catalyzed asymmetric cyclopropanation of dehydroaminocarboxylates with diazo compounds offers a potentially attractive approach for stereoselective

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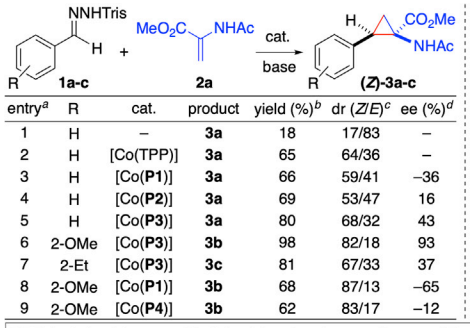
synthesis of valuable chiral cyclopropyl α-amino acid derivatives. However, there have been only a few reports on metal-based catalytic systems for direct synthesis of cyclopropyl α-amino acid derivatives from dehydroaminocarboxylates.[13] It was shown that control of diastereoselectivity in cyclopropanation reactions of 1,1-disubstituted alkenes, such as dehydroaminocarboxylates, is typically more challenging than those of monosubstituted alkenes.[13b,14] In addition to their moderate diastereoselectivity and limited scopes, none of the reported systems involved the control of enantioselectivity. The underdevelopment of this potentially useful catalytic method is attributed to the electronic incompatibility of dehydroaminocarboxylates as electron-deficient alkenes with the existing catalytic systems involving electrophilic metallocarbene intermediates.[13a,13b,15] When donor-substituted diazo compounds such as α-aryldiazomethanes are used as carbene sources, the development of asymmetric catalytic system poses additional challenges due to competitive uncatalyzed thermal process via [3+2] cycloaddition.[13b,16a] To circumvent the difficulty, Aggarwal and co-workers reported an innovative solution that relied upon the combined use of dirhodium tetracarboxylates and chiral sulfides as dual catalysts to transfer the initially generated electrophilic Rh_2-carbenes into nucleophilic chiral sulfur ylides as demonstrated for asymmetric cyclopropanation of dehydroaminocarboxylate substrates with *in situ*-generated α-phenyldiazomethane.[17] Davies and co-workers developed an alternative approach for stereoselective syntheses of chiral cyclopropyl α-amino acid derivatives that was based on Rh_2-catalyzed asymmetric cyclopropanation of alkenes with vinyldiazomethanes, followed by oxidation.[18a] As another alternative approach, Charette and co-workers synthesized chiral cyclopropyl α-amino acid derivatives through reduction of enantioenriched α-nitrocyclopropanecarboxylates that were formed by Rh_2- and Cu-catalyzed asymmetric olefin cyclopropanation.[18b–18f] Evidently, a new catalytic system that is fundamentally different from the existing catalytic systems involving electrophilic metallocarbene intermediates might be needed in order to achieve direct asymmetric cyclopropanation of dehydroaminocarboxylates, a stereoselective transformation that has not been previously developed. We herein report the application of Co(II)-based metalloradical catalysis (MRC) for the development of a new catalytic radical process that is highly effective for asymmetric cyclopropanation of dehydroaminocarboxylates with *in situ*-generated α-aryldiazomethanes. Supported by an optimal D_2-symmetric chiral amidoporphyrin ligand, the Co(II)-based catalytic system is applicable to broad combinations of α-aryldiazomethanes and dehydroaminocarboxylates. In addition to high yields and excellent enantioselectivities, the Co(II)-catalyzed asymmetric cyclopropanation enables direct synthesis of α-amino-β-arylcyclopropanecarboxylates with (*Z*)-diastereoselectivity, which is different from uncatalyzed thermal reaction.[13b,16a]

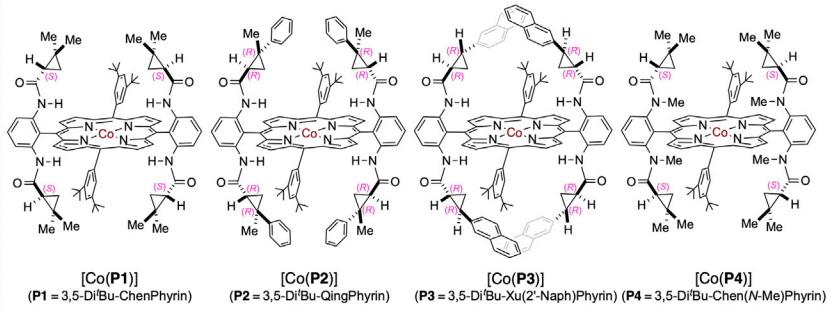
RESULTS AND DISCUSSION

Reaction development

Our effort started with the investigation of cyclopropanation reaction of dehydroaminocarboxylate **2a** as the model substrate with *in situ*-generated α-phenyldiazomethane (**1a'**) from the combination of benzaldehyde trisylhydrazone **1a** and Cs_2CO_3 using Co(II)-based metalloradical catalysts (Figure 1). In line with literature reports,[13b,16a] the reaction occurred even at 4°C in the absence of a catalyst, producing the corresponding cyclopropane **3a** in 18% yield with 17/83 dr in favor of the (*E*)-diastereomer (Figure 1; entry 1). When the simple metalloradical catalyst [Co(TPP)] (TPP = 5,10,15,20-tetraphenylporphyrin) was used, the desired cyclopropane **3a** was generated in 65% yield with a 64/36 dr preference for the opposite (*Z*)-diastereomer, implying the domination of catalyst-controlled process over the



entry[a]	R	cat.	product	yield (%)[b]	dr (*Z*/*E*)[c]	ee (%)[d]
1	H	–	**3a**	18	17/83	–
2	H	[Co(TPP)]	**3a**	65	64/36	–
3	H	[Co(**P1**)]	**3a**	66	59/41	–36
4	H	[Co(**P2**)]	**3a**	69	53/47	16
5	H	[Co(**P3**)]	**3a**	80	68/32	43
6	2-OMe	[Co(**P3**)]	**3b**	98	82/18	93
7	2-Et	[Co(**P3**)]	**3c**	81	67/33	37
8	2-OMe	[Co(**P1**)]	**3b**	68	87/13	–65
9	2-OMe	[Co(**P4**)]	**3b**	62	83/17	–12



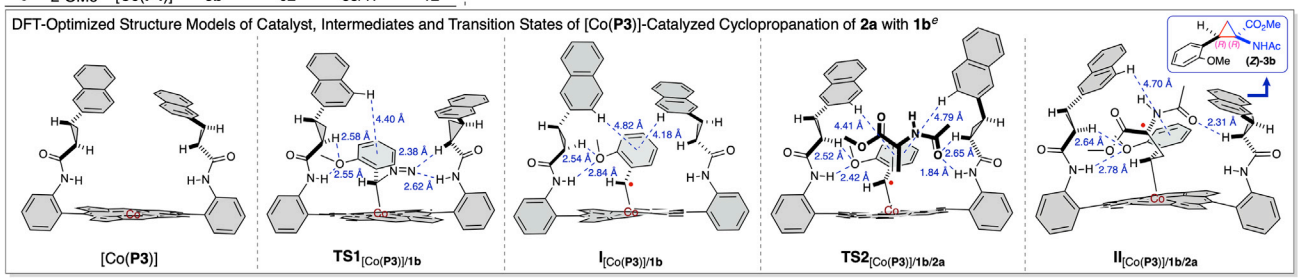


Figure 1. Ligand effect on Co(II)-based catalytic system for asymmetric cyclopropanation of dehydroaminocarboxylates with α-aryldiazomethanes

[a]Conducted with **1** (0.12 mmol), **2** (0.10 mmol), and Cs_2CO_3 (0.24 mmol) using Co(II) catalyst (2 mol %) in chlorobenzene at 4°C for 12 h.

[b]Isolated yields.

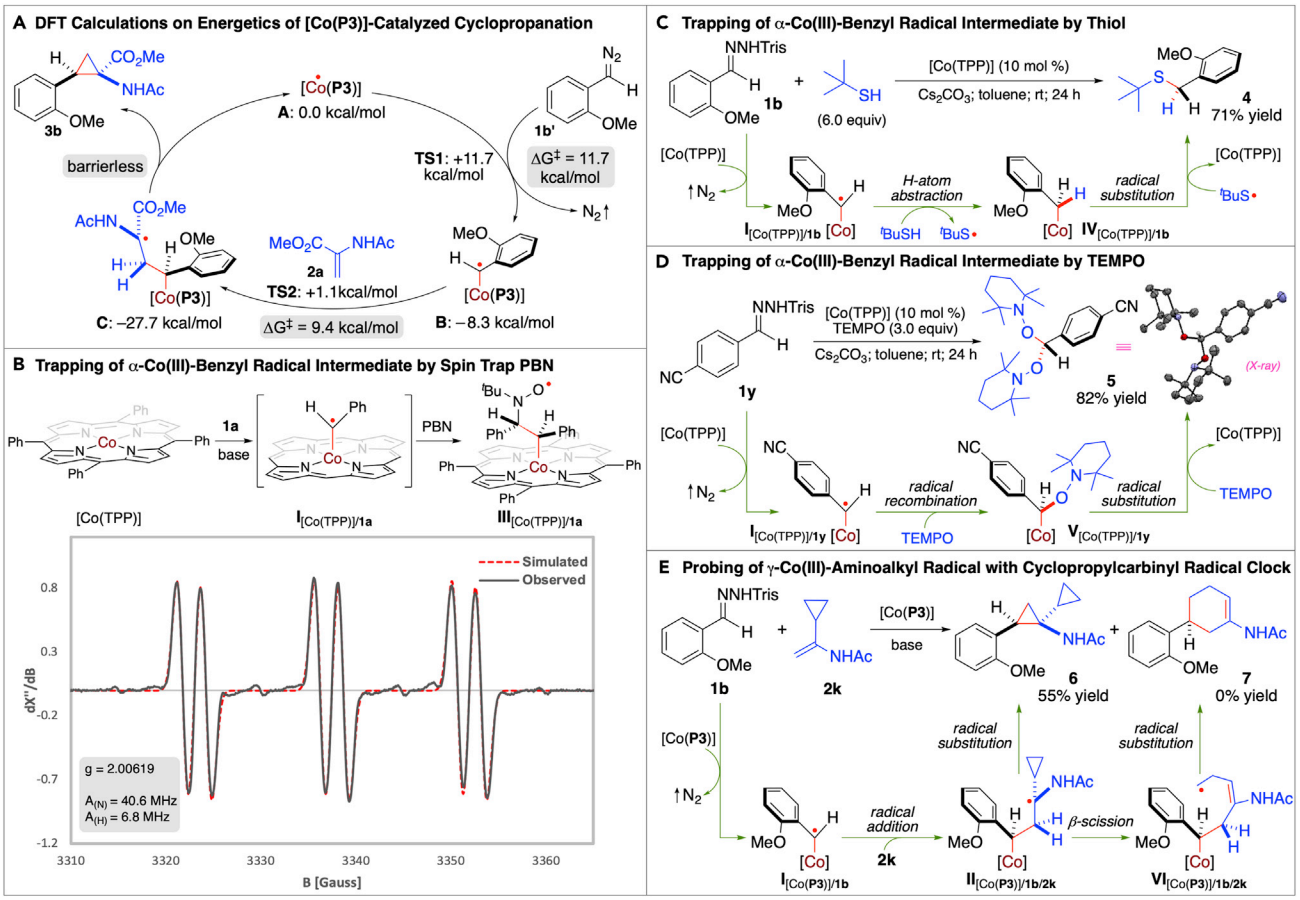
[c]Diastereomeric ratio (dr) determined by ^{1}H NMR analysis of reaction mixture.

[d]Enantiomeric excess (ee) of major (*Z*)-isomer determined by chiral HPLC.

[e]DFT-optimized models showing H-bonding and π-stacking interactions; Substituents on the bottom side, as well as at the inside and outside *meso* positions, omitted for clarity; see Scheme 2 and Supplemental information for details. Tris = 2,4,6-triisopropylbenzenesulfonyl.

competitive thermal reaction (Figure 1; entry 2). This initial result inspired us to explore the possibility of achieving enantioselectivity in the Co(II)-catalyzed reaction with the use of D_2-symmetric chiral amidoporphyrins as the supporting ligands. To our delight, when first-generation chiral metalloradical catalyst [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-ChenPhyrin)[8a] was employed, cyclopropyl α-amino ester **3a** was formed in a similar yield with significant enantioselectivity despite diminished (*Z*)-diastereoselectivity (Figure 1; entry 3). Changing [Co(**P1**)] to second-generation chiral metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-QingPhyrin)[8g] switched the asymmetric induction in favor of the opposite enantiomer albeit with lower enantioselectivity (from –36% ee to 16% ee) without significantly affecting the product yield and diastereoselectivity (Figure 1; entry 4).

To further improve the enantioselectivity of the catalytic process, we then turned our attention to another second-generation metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-Xu(2′-Naph)Phyrin) containing naphthyl groups in the chiral amide units,[19] which could potentially enhance π-stacking interaction with the phenyl group in the corresponding α-Co(III)-benzyl radical intermediate $I_{[Co(P3)]/1a}$ for achieving conformational rigidity (Figure 1). As expected, the catalytic reaction by [Co(**P3**)] afforded (*Z*)-**3a** in a better yield (80%) along with higher diastereoselectivity and enantioselectivity (68/32 dr; 43% ee) (Figure 1; entry 5). This positive outcome prompted us to install potential H-bonding interaction as an additional rigidification element for the conformation of intermediate $I_{[Co(P3)]}$. Inspired by our previous report,[8i] we decided to explore the use of *o*-methoxybenzaldehyde trisylhydrazone **1b** to generate the corresponding radical precursor for catalytic cyclopropanation of dehydroaminocarboxylate **2a** by [Co(**P3**)]. As illustrated in the DFT-optimized structure models (Figure 1; see Scheme 2 and Supplemental information for details), installation of –OMe group at the *ortho*-position of



Scheme 2. Computational and experimental studies on reaction pathway of Co(II)-catalyzed cyclopropanation of dehydroaminocarboxylates

the α-Co(III)-benzyl radical intermediate $I_{[Co(P3)]/1b}$ gives rise to multiple H-bonding and related interactions, in addition to the double π-stacking interactions, which together rigidify the radical intermediate's conformation. The DFT calculations also reveal multiple H-bonding and π-stacking interactions in both the transition state for the generation of intermediate $I_{[Co(P3)]/1b}$ ($TS1_{[Co(P3)]/1b}$) and the transition state for its subsequent radical addition with dehydroaminocarboxylate **2a** ($TS2_{[Co(P3)]/1b/2a}$). Furthermore, it shows the existence of H-bonding and π-stacking interactions in the resulting γ-Co(III)-aminoalkyl radical $II_{[Co(P3)]/1b/2a}$ as well. According to the DFT models, it would lead to the preferred formation of the corresponding cyclopropane product **3b** as (*Z*)-diastereomer with (1*R*,2*R*) configuration (Figure 1). In addition to the conformational rigidification of the intermediates, these noncovalent attractive interactions can cooperatively lower the activation barriers of the transition states (see Scheme 2), which may enhance catalytic reactivity and improve stereoselectivities of the product. Excitingly, the cyclopropanation reaction of dehydroaminocarboxylate **2a** with *o*-methoxybenzaldehyde trisylhydrazone **1b** by [Co(**P3**)] indeed delivered the desired chiral cyclopropyl α-amino ester **3b** in excellent yield (98%) with higher (*Z*)-diastereoselectivity (82/18 dr) and excellent enantioselectivity (93% ee) (Figure 1; entry 6). As suggested by the DFT model of γ-Co(III)-aminoalkyl radical $II_{[Co(P3)]/1b/2a}$, cyclopropane **3b** was produced preferentially as (*Z*)-diastereomer with (1*R*,2*R*) configuration (see Figure 2). In accordance with the postulation, when *o*-methoxybenzaldehyde hydrazone **1b** was replaced by sterically comparable *o*-ethylbenzaldehyde hydrazone 1c, the observed enhancement in both reactivity and selectivity vanished completely (Figure 1; entry 7), giving the corresponding chiral

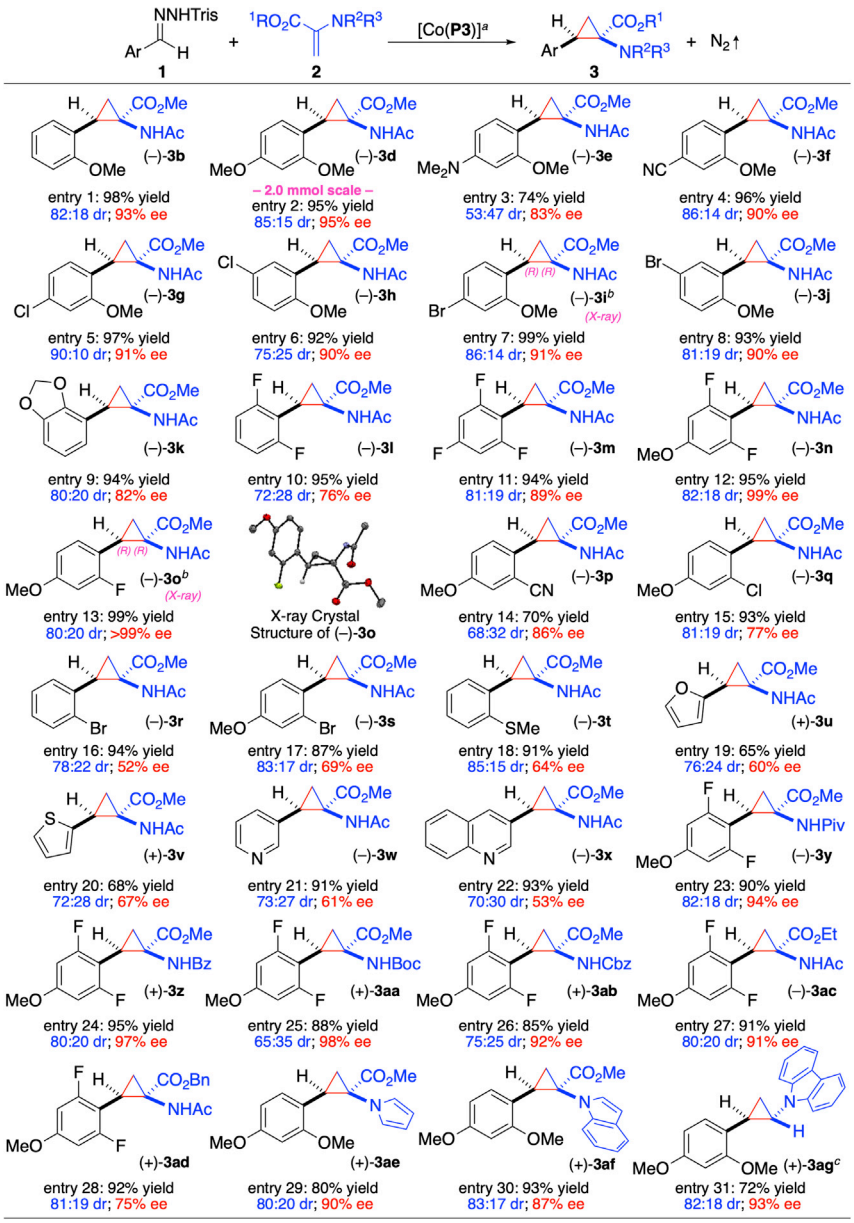


Figure 2. Substrate scope of asymmetric cyclopropanation of dehydroaminocarboxylates with α-aryldiazomethanes catalyzed by [Co(P3)]

[a]Conducted with **1** (0.12 mmol), **2** (0.10 mmol), and Cs_2CO_3 (0.24 mmol) using [Co(**P3**)] catalyst (2 mol %) in chlorobenzene at 4°C for 12 h; Isolated yields; Diastereomeric ratio (dr) determined by ^{1}H NMR analysis of reaction mixture; Enantiomeric excess (ee) of major (*Z*)-isomer determined by chiral HPLC.

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

[c]In methanol at 23°C.

cyclopropyl α-amino ester (*Z*)-**3c** in the same yield with similar stereoselectivities as those obtained with non-substituted **1a** (Figure 1; entry 5). To further examine the effect of noncovalent interactions such as H-bonding interaction on reactivity and selectivity, a new catalyst [Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-Chen(*N*-Me)Phyrin) was prepared by methylation of the four amide units in [Co(**P1**)] and then employed for comparative study on catalytic cyclopropanation of dehydroaminocarboxylate **2a** with *o*-methoxybenzaldehyde

trisylhydrazone **1b** (Figure 1; entries 8 and 9). It was found that both diastereoselectivity and enantioselectivity as well as yield of the desired cyclopropane product **3b** were diminished when change the catalyst from [Co(**P1**)] to [Co(**P4**)], indicating the important role of H-bonding interaction.

Substrate scope

Under the optimized conditions, the scope of [Co(**P3**)]-catalyzed asymmetric cyclopropanation of dehydroaminocarboxylates was then evaluated by employing various aromatic aldehyde-derived sulfonylhydrazones (Figure 2). Like α-(*o*-methoxy) phenyldiazomethane from hydrazone **1b**, different α-aryldiazomethanes bearing *o*-OMe group, which were *in situ* generated from the derivatives of *o*-methoxybenzaldehyde hydrazone, could also be effectively activated by [Co(**P3**)] for asymmetric cyclopropanation of dehydroaminocarboxylate **2a**. For example, hydrazones derived from *o*-methoxybenzaldehydes containing both electron-donating groups (–OMe and $–NMe_2$) and electron-withdrawing group (–CN) at the *para*-position could be employed to cyclopropanate **2a** in the presence of Cs_2CO_3, generating the desired cyclopropyl α-amino ester **3d–3f** in high yields with varied (*Z*)-diastereoselectivities and high enantioselectivities (Figure 2; entries 2–4). As well, the Co(II)-based system could successfully use *o*-methoxybenzaldehyde hydrazones with halogen substituents, such as –Cl and –Br atoms at different positions for the cyclopropanation process, forming the halogenated (*Z*)-cyclopropanes **3g–3j** in similarly high yields with good diastereoselectivities and high enantioselectivities (Figure 2; entries 5–8). Although the exact reason is unclear, the significantly lower diastereoselectivity observed for **3e** than **3g** might be attributed to potential role of *p*-NMe_2 group as H-bonding acceptor, which could interfere with desired H-bonding interaction of the *o*-OMe group. It was found that benzodioxole aldehyde-derived hydrazone **1k** was also suitable for the catalytic process, producing the fused-arylcyclopropane **3k** in high yield and stereoselectivities (Figure 2; entry 9).

In addition to the observed positive effect of *o*-OMe group, α-aryldiazomethanes bearing *o*-F atoms were also found to be effective metalloradicophiles for [Co(**P3**)]-catalyzed asymmetric cyclopropanation of dehydroaminocarboxylate **2a**. For instance, hydrazones derived from both 2,6-difluorobenzaldehyde (**1l**) and 2,4,6-trifluorobenzaldehyde (**1m**) could be productively utilized to furnish fluorinated cyclopropane **3l** and **3m** (Figure 2; entries 10 and 11). Interestingly, placing electron-donating –OMe group at the *para*-position further boosted both reactivities and stereoselectivities as shown with the formation of cyclopropane **3n** and **3o** in near quantitative yields with almost perfect control of enantioselectivities (Figure 2; entries 12 and 13). Surprisingly, with the presence of electron-donating –OMe group at the *para*-position, even *ortho*-CN and *ortho*-Cl benzaldehyde hydrazones were suitable for asymmetric cyclopropanation by [Co(**P3**)], generating products **3p** and **3q** (Figure 2; entries 14 and 15) in good yields and stereoselectivities. Furthermore, α-aryldiazomethanes containing other *ortho*-substituents that are potentially removable, such as –Br and –SMe groups, could also be effectively employed for asymmetric cyclopropanation of dehydroaminocarboxylate **2a**, delivering the desired cyclopropanes **3r–3t** in similarly high yields with good diastereoselectivities albeit lower enantioselectivities (Figure 2; entries 16–18).

To further challenge the catalytic system, we then explored the possibility of employing α-heteroaryldiazomethanes as radical precursors for asymmetric cyclopropanation of dehydroaminocarboxylates by [Co(**P3**)] in view of the potential role of the heteroatoms as H-bonding acceptors. It was thrilling to find out that furan-2-carbaldehyde-derived trisylhydrazone (**1u**) could be productively employed

for the asymmetric cyclopropanation of **2a** to form the desired cyclopropane (*Z*)-**3u** with promising level of stereoselectivities (Figure 2; entry 19). Furthermore, hydrazone **1v** derived from thiophene-2-carbaldehyde could also be applied to cyclopropanate **2a**, furnishing cyclopropane (*Z*)-**3v** with better enantioselectivity (Figure 2; entry 20). In addition to the *O*- and *S*-heteroaryldiazomethanes, *N*-heteroaryldiazomethanes generated *in situ* from the hydrazone precursors were found to be also effective for [Co(**P3**)]-catalyzed asymmetric cyclopropanation of **2a** as demonstrated with the high-yielding formation of pyridine- and quinoline-containing (*Z*)-cyclopropanes **3w** and **3x** with similarly promising stereoselectivities (Figure 2; entries 21 and 22). It should be noted that α-heteroaryldiazomethanes based on benzofuran and *N*-Boc-indole were found to be much less effective for the catalytic process, presumably due to their reduced abilities as H-bonding acceptors.

Besides the acyl group in **2a**, dehydroaminocarboxylates bearing various other amino protecting groups, such as –Piv, –Bz, –Boc, and –Cbz, were all suitable substrates for the Co(II)-based system, affording the corresponding (*Z*)-α-aminocyclopropanecarboxylates **3y–3ab** in similarly high yields with the same high level of enantioselectivities (Figure 2; entries 23–26). Besides methyl esters, the catalytic cyclopropanation could be applied for other esters of dehydroaminocarboxylates as demonstrated with stereoselective production of ethyl ester **3ac** (Figure 2; entry 27) and benzyl ester **3ad** (Figure 2; entry 28) of cyclopropyl α-amino acids in high yields. However, dehydroaminocarboxylates with *N*-Ts protecting group were found to be ineffective substrates, likely due to the increased steric hinderance. It is noted that changing the steric hindrance of the amino protecting group and the ester group in dehydroaminocarboxylates had different effects on diastereoselectivity of the resulting α-aminocyclopropanecarboxylate products. While changing the ester group of dehydroaminocarboxylates seemed have almost no effect (Figure 2; entry 12: 82:18 dr for Me ester; entry 27: 80:20 dr for Et ester; entry 28: 81:19 dr for Bn ester), more pronounced effect was observed with different *N*-protecting groups. Although changing of the *N*-protecting groups from *N*-Ac (Figure 2; entry 12: 82:18 dr) to *N*-Piv (Figure 2; entry 23: 82:18 dr) to *N*-Bz (Figure 2; entry 24: 80:20 dr) had little effect on diastereoselectivity, significant decrease in diastereoselectivity was observed with both *N*-Boc group (Figure 2; entry 25: 65:35 dr) and *N*-Cbz group (Figure 2; entry 26: 75:25 dr). In general, the level of diastereoselectivity seems depend on the difference in the relative overall size between the amino protecting group and the ester group.

In addition to dehydroaminocarboxylates with protected secondary amines, the [Co(**P3**)]-catalyzed asymmetric cyclopropanation could even be applicable to dehydroaminocarboxylate substrates bearing cyclic tertiary amine functionalities at the vinyl position. For examples, cyclopropyl α-amino acids **3ae** and **3af** could be formed in high yields with high enantioselectivities and good diastereoselectivities from the reactions of dehydroaminocarboxylates containing pyrrole and indole heteroaryl functionalities, respectively (Figure 2; entries 29 and 30). Interestingly, when *N*-vinylcarbazole, which contains cyclic tertiary carbazole functionality at the vinyl position without the geminal ester group, was used as a substrate for the catalytic system, it could also form the corresponding cyclopropane **3ag** in good yield with similarly high diastereoselectivity and enantioselectivity (Figure 2; entry 31). However, when dehydroaminocarboxylate bearing azide group at the vinyl position was used as the substrate, the catalytic reaction gave a mixture of unidentifiable products without observation of the corresponding cyclopropane, presumably due to the involvement of the azide unit in the catalytic reaction.

It is worth noting that the catalytic process could be readily scaled up under the same conditions as exemplified by the synthesis of cyclopropyl α-amino ester (*Z*)-**3d** in high yield and stereoselectivities on 2.0 mmol scale (Figure 2; entry 2). The absolute configurations of cyclopropyl α-amino esters **3i** and **3o** were both determined as (1*R*,2*R*) by X-ray crystallography (Figure 2; entries 7 and 13), which is consistent with the DFT models (Figure 1).

Mechanistic studies

In addition to the optimized structure models of α-Co(III)-benzyl radical intermediate $I_{[Co(P3)]/1b}$ and γ-Co(III)-aminoalkyl radical $II_{[Co(P3)]/1b/2a}$, as well as associated transitional states $TS1_{[Co(P3)]/1b}$ and $TS2_{[Co(P3)]/1b/2a}$ (Figure 1), we carried out further DFT calculations on the energetics associated with the catalytic pathway for the cyclopropanation reaction of dehydroaminocarboxylate **2a** with *o*-methoxyphenyldiazomethane **1b′** by [Co(**P3**)] (Scheme 2A; see Supplemental information for details). The DFT calculations indicate that the formation of α-Co(III)-benzyl radical intermediate **B** ($I_{[Co(P3)]/1b}$) upon activation of diazo **1b′** by [Co(**P3**)] is exergonic by –8.3 kcal/mol, with the elimination of dinitrogen as the byproduct. The metalloradical activation has a relatively low activation barrier (**TS1**: $\Delta G^{\ddagger}$ = 11.7 kcal/mol) and represents the rate-determining step. The subsequent radical addition of radical intermediate **B** to alkene **2a**, which is highly exergonic by –19.4 kcal/mol, has an even lower activation barrier (**TS2**: $\Delta G^{\ddagger}$ = 9.4 kcal/mol), leading to the formation of γ-Co(III)-aminoalkyl radical intermediate **C** (Scheme 2A). According to the DFT calculations, the final step of *3-exo-tet* cyclization through radical substitution, which is exergonic by –14.3 kcal/mol, is found to be an almost barrierless process, leading to the formation of the corresponding cyclopropane **3b** and the regeneration of the catalyst [Co(**P3**)]. The overall low activation barrier is consistent with the fact that the catalytic reaction could proceed effectively even at 4°C.

While the initially formed key α-Co(III)-alkyl radical intermediates were previously observed spectroscopically,[7,8] we were interested in the possibility of directly trapping the Co-supported benzyl radicals with different methods. To trap the α-Co(III)-benzyl radical intermediate **I** for detection, we first added spin trapping reagent PBN (*N*-*tert*-butyl-α-phenylnitrone) into a reaction mixture of [Co(TPP)] with hydrazone **1a** in benzene in the absence of alkene substrate and then recorded the X-band electron paramagnetic resonance (EPR) spectrum at room temperature (Scheme 2B). The isotropic EPR spectrum displays the characteristic triplet of doublet signals at g value of ~2.00, which was taken as the evidence for the formation of radical $III_{[Co(TPP)]/1a}$ from PBN trapping of the initially generated α-Co(III)-benzyl radical $I_{[Co(TPP)]/1a}$. The observed spectrum could be fittingly simulated on the basis of the hyperfine couplings by ^{14}N (I = 1) and ^{1}H (I = 1/2) at g value of 2.00619 with $A_{(N)}$ = 40.6 MHz and $A_{(H)}$ = 6.8 MHz. Subsequently, α-(*o*-methoxy)phenyldiazomethane from hydrazone **1b** was allowed to react with [Co(TPP)] without olefin substrates but in the presence of *tert*-butylthiol as H-atom source (Scheme 2C). After the reaction, compound **4** was isolated in 71% yield and characterized as *tert*-butyl(2-methoxybezyl)sulfane. The formation of thioether **4** can be conceived to proceed through a sequence of radical H-atom abstraction from *tert*-butylthiol by α-Co(III)-benzyl radical intermediate $I_{[Co(TPP)]/1b}$ and subsequent radical substitution of the resulting Co(III)-benzyl complex $IV_{[Co(TPP)]/1b}$ by *tert*-butyl thiyl radical (Scheme 2C). In addition to H-atom abstraction from H-atom sources such as *tert*-butylthiol, efforts were made to directly trap the metal-supported benzyl radical intermediates by stable 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) radical (Scheme 2D). After α-(*p*-cyano)phenyldiazomethane from hydrazone **1y** was reacted with [Co(TPP)] in the presence of TEMPO, we were thrilled to isolate a new product 5 in high yield

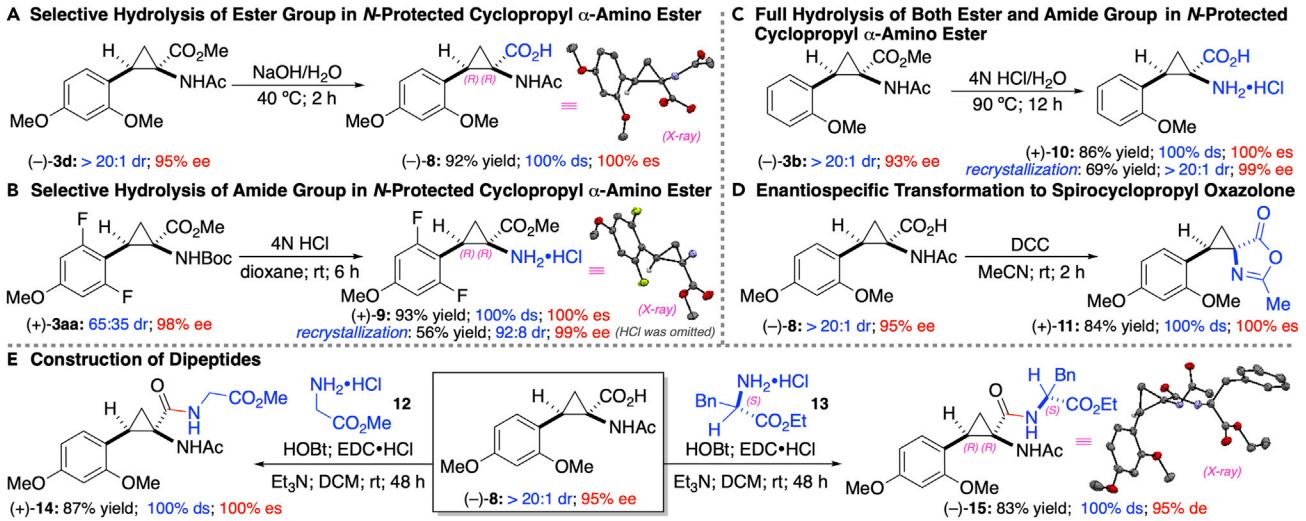
(82%), whose structure contains two geminal TEMPO units at the α-position of *p*-cyanotoluene as confirmed by X-ray crystallography. The formation of bis(TEMPO)methane derivative **5** indicated the existence of the initial α-Co(III)-benzyl radical intermediate $I_{[Co(TPP)]/1y}$ from metalloradical activation of the α-aryldiazomethane by [Co(TPP)]. Evidently, radical intermediate $I_{[Co(TPP)]/1y}$ was trapped by TEMPO to form Co(III)-benzyl complex $V_{[Co(TPP)]/1y}$, which further underwent radical substitution by another molecule of TEMPO to deliver the final product **5** (Scheme 2D). It is worth noting that compound **5** represents the first isolated example of such compounds that contain two geminal TEMPO substituents.

Furthermore, *N*-vinylacetamide **2k** bearing a geminal cyclopropyl ring was employed as a radical-clock substrate to probe the lifetime of the corresponding γ-Co(III)-aminoalkyl radical intermediate $II_{[Co(P3)]/1b/2k}$ in the catalytic cyclopropanation reaction with hydrazone **1b** by [Co(**P3**)] (Scheme 2E). It was found that the cyclopropanation reaction of **2k** with **1b** generated the corresponding 1,1′-linked bicyclopropane **6** in 55% yield with no formation of *N*-cyclohexenylacetamide product **7**, a potential product that would be expected from ring opening of cyclopropylcarbinyl radical intermediate. Conceivably, γ-Co(III)-aminoalkyl radical intermediate $II_{[Co(P3)]/1b/2k}$, which was formed from radical addition of the initially generated α-Co(III)-benzyl radical intermediate $I_{[Co(P3)]/1b}$ with **2k**, underwent facile *3-exo-tet* radical cyclization via radical substitution to form product 6 at a reaction rate that was even faster than the ring opening of tertiary cyclopropylcarbinyl radicals for generation of ζ-Co(III)-alkyl radical intermediate $VI_{[Co(P3)]/1b/2k}$. This experimental observation seems in good agreement with the result of DFT calculations that suggests a barrierless step of radical substitution (Scheme 2A).

Synthetic applications

Among potential applications, the resulting enantioenriched (*Z*)-α-aminocyclopropanecarboxylates from the Co(II)-based catalytic process may serve as non-proteinogenic α-amino acid building blocks for the synthesis of peptides with restricted conformations. It would be practically important for this application that *N*-protected cyclopropyl α-amino esters **3** could be selectively or fully deprotected through controlled hydrolysis to provide *N*-protected cyclopropyl α-amino acids, *N*-unprotected cyclopropyl α-amino esters or fully unprotected cyclopropyl α-amino acids without affecting the original stereoisomeric purities. To this end, we showed that methyl ester in **3d** could be selectively hydrolyzed under mild basic conditions, affording *N*-protected cyclopropyl α-amino acid **8** in 92% yield with 100% es and 100% ds (Scheme 3A). The free acid functionality in compound **8** was further confirmed by X-ray crystallography. On the other hand, when the hydrolysis was conducted under mild acidic conditions, the *N*-Boc-group in **3aa** could be selectively removed to furnish cyclopropyl α-amino ester **9** in 93% yield with 100% es and 100% ds, which could be further enriched by recrystallization to provide **9** with 92:8 dr and 99% ee (Scheme 3B). The free amino group in compound **9** was further confirmed by X-ray crystallography. Full hydrolysis of both amide and ester groups could be achieved under acidic conditions at an elevated temperature as demonstrated for the production of cyclopropyl α-amino acid **10** in 86% yield with 100% es and 100% ds, enantiopurity of which could be increased to 99% ee upon recrystallization (Scheme 3C).

Furthermore, *N*-protected cyclopropyl α-amino acid **8** was readily cyclized in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to deliver spirocyclopropyl oxazolone **11** in 84% yield with 100% es and 100% ds (Scheme 3D). In addition to their known bioactivities such as anti-HIV and anti-herpes protease activities,[20a,20b]



Scheme 3. Synthetic applications of enantioenriched (Z)-α-aminocyclopropanecarboxylates

spirocyclopropyl oxazolones like **11** were also demonstrated as building blocks for the synthesis of peptides.[20c] To demonstrate the potential applications for conformationally rigid peptides, we showcased the synthesis of two dipeptides from enantioenriched *N*-protected cyclopropyl α-amino acid **8** (Scheme 3E). When **8** was coupled with glycine methyl ester hydrochloride (**12**) and L-phenylalanine ethyl ester hydrochloride (**13**) using the combination of hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride under basic conditions, it afforded dipeptides **14** and **15**, respectively, in high yields with full retention of the original stereochemistry. As revealed by X-ray crystallography, dipeptide **15** has constrained ϕ- and ψ-torsion angles of 77 and 17 degrees, respectively. This constrained structural property, together with relative and absolute stereochemistry, may result in profound changes in conformation, stability, and bioactivity of peptidomimetics incorporated with cyclopropyl α-amino acid units.[11d,11e,12e,12f]

Conclusions

In summary, we have developed the first asymmetric catalytic system for direct cyclopropanation of dehydroaminocarboxylates with *in situ*-generated α-aryldiazomethanes via Co(II)-based metalloradical catalysis (MRC). With D_2-symmetric chiral amidoporphyrin 3,5-Di^{t}Bu-Xu(2′-Naph)Phyrin as the optimal supporting ligand, the Co(II)-based metalloradical system enables stereoselective synthesis of (*Z*)-α-aminocyclopropanecarboxylates directly from dehydroaminocarboxylates in high yields with high enantioselectivities under mild conditions. Mechanistically, the detailed pathway of the underlying stepwise radical mechanism of Co(II)-based metalloradical cyclopropanation has been elucidated by DFT study, revealing the importance of cooperative noncovalent interactions such as multiple H-bonding and π-stacking offered by the ligand environment of 3,5-Di^{t}Bu-Xu(2′-Naph)Phyrin. In addition to computational elucidation, the key intermediate α-Co(III)-benzyl radicals have, for the first time, been directly trapped by thiol and TEMPO and experimentally characterized. As showcased for the efficient synthesis of dipeptides, it is our hope that the resulting enantioenriched (*Z*)-α-amino-β-arylcyclopropanecarboxylates from this newly developed asymmetric process will find applications as a unique class of non-proteinogenic α-amino acid building blocks for the design and

synthesis of novel peptides with restricted conformations that may have interesting biological properties.

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 compounds (1*R*,2*R*)-**3i**, (1*R*,2*R*)-**3o**, **5**, (1*R*,2*R*)-**8**, (1*R*,2*R*)-**9**, and (1*R*,2*R*,*S*)-**15** have been deposited in the Cambridge structural database under reference numbers CCDC: 2043163, 2043164, 2043165, 2043166, 2043167, and 20431638, 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.2021.03.002.

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AUTHOR CONTRIBUTIONS

W.-C.C.L. conducted the experiments. D.-S.W. performed the DFT calculations. C.Z. and J.X. assisted the experiments. B.L. carried out the X-ray crystallography. X.P.Z. conceived the work and directed the project. W.-C.C.L. and X.P.Z. designed the experiments and wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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