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Asymmetric Radical Bicyclization for Stereoselective Construction of Tricyclic Chromanones and Chromanes with Fused Cyclopropanes

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Abstract

Asymmetric radical bicyclization processes have been developed via metalloradical catalysis (MRC) to stereoselectively construct chiral chromanones and chromanes bearing fused cyclopropanes. Through optimization of a versatile D_2-symmetric chiral amidoporphyrin ligand platform, a Co(II)-metalloradical system can homolytically activate both diazomalonates and α-aryldiazomethanes containing different alkene functionalities under mild conditions for effective radical bicyclization, delivering cyclopropane-fused tricyclic chromanones and chromanes, respectively, in high yields with excellent control of both diastereoselectivities and enantioselectivities. Combined computational and experimental studies, including the electron paramagnetic resonance (EPR) detection and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) trapping of key radical intermediates, shed light on the working details of the underlying stepwise radical mechanisms of the Co(II)-catalyzed bicyclization processes. The two catalytic

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Experimental details and analytical data for all new compounds (PDF)

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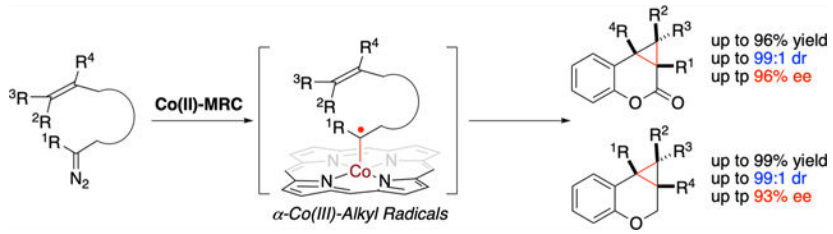
radical processes provide effective synthetic tools for stereoselective construction of valuable cyclopropane-fused chromanones and chromanes with newly generated contiguous stereogenic centers. As a specific demonstration of synthetic application, the Co(II)-catalyzed radical bicyclization has been employed as a key step for the first asymmetric total synthesis of the natural product (+)-Radulanin J.

Graphical Abstract



INTRODUCTION

One-electron radical reactions have been considerably less utilized than two-electron polar reactions in organic synthesis even though radical chemistry is known for being both rich in fundamental reactivities and attractive with practical attributes. This lag in development is attributed to the long-standing challenges associated with the control of reactivity and stereoselectivity of highly active free radicals, especially regarding enantioselectivity as inversion between two prochiral faces of radical intermediates is typically facile.[1] In order to harness the untapped potential of homolytic radical chemistry for stereoselective construction of molecular structures, it calls for formulation of new concepts and establishment of different strategies to command the control of both generation and reaction of active radical intermediates.[2] Within this context, metalloradical catalysis (MRC), which exploits metal-centered radicals as one-electron catalysts for homolytic activation of substrates to generate metal-entangled organic radicals as key intermediates, has emerged as a powerful catalytic approach to achieving the control of both reactivity and stereoselectivity in radical reactions.[3–5] Cobalt(II) complexes of porphyrins [Co(Por)], as a family of stable 15e-metalloradicals, have demonstrated an unusual aptitude for homolytic activation of diazo compounds to generate α-Co(III)-alkyl radical intermediates, a class of metal-bonded, carbon-centered organic radicals that can undergo common types of radical reactions but in a catalytic and controlled manner.[6] With the introduction of D_2-symmetric chiral amidoporphyrins as the ligand platform,[7] Co(II)-based metalloradical catalysts [Co(D_2-Por*)] have proven highly effective in homolytically activating different classes of diazo compounds for asymmetric intermolecular cyclopropanation of various alkenes via stepwise radical mechanism.[8] More recently, it was shown that both diazomalonates (acceptor/acceptor-substituted diazo compounds) and in situ-generated α-aryldiazomethanes (donor/hydrogen-substituted diazo compounds) could function as potent metalloradicophiles for Co(II)-based MRC to cyclopropanate alkenes in an intermolecular fashion, delivering chiral cyclopropanes with effective control of stereoselectivities.[8h–j] Prompted by these recent findings, we were intrigued to the possibility of refashioning the catalytic transformations

into intramolecular processes for radical bicyclization with the use of diazomalonates and α-aryldiazomethanes that contain dangling alkene functionalities.

We were particularly interested in exploring the potential application of Co(II)-based MRC for asymmetric radical bicyclization of 2-vinylaryl diazomalonates **1** and in situ-generated α-(2-(allyloxy)aryl)diazomethanes **3′** to stereo-selectively construct the structurally related cyclopropane-fused chromanones **2** and chromanes **4**, respectively, in view of their biological importance (Scheme 1).[9] While metalloradical activation of both diazomalonates **1** and α-aryldiazomethanes **3′** was foreseen to proceed readily, it was uncertain whether the intramolecular radical addition of the initially generated α-Co(III)-malonyl radical intermediate **I** (Scheme 1A) and α-Co(III)-benzyl radical intermediate **III** (Scheme 1B) could be negatively impacted by the steric hinderance associated with the substituents. Mechanistically, there are two intramolecular pathways for both intermediates **I** and **III** to proceed the following step of radical addition: *6-exo-trig* versus *7-endo-trig*. It was unclear what would be the preferred pathway to undergo the radical cyclization. Conceivably, this regioselectivity issue would closely connect with the control of enantioselectivity for the overall catalytic process since the radical cyclization creates the first stereogenic center. To achieve the control of enantioselectivity, it was foreseeable that α-Co(III)-malonyl radical **I** (Scheme 1A) and α-Co(III)-benzyl radical **III** (Scheme 1B) might require different ligand environments in order to discriminate the two prochiral faces of the respective alkene unit. Furthermore, it was unsure if the resulting γ-Co(III)-alkyl radicals **II** and **IV** could smoothly undergo the desired *3-exo-tet* radical cyclization to produce chromanones **2** and chromanes **4**, respectively, while creating the contiguous stereogenic centers on the fused cyclopropane ring with stereoselectivity, considering the highly strained nature of the tricyclic structures. We envisioned to address these and related challenges through catalyst innovation by designing a D_2-symmetric chiral amidoporphyrin ligand with proper steric, electronic, and chiral environment that promotes the radical process while governing the stereochemical course. If successfully implemented, it would lead to the invention of new synthetic tools for stereoselective construction of chiral cyclopropane-fused chromanones and chromanes, which occur as the common structures in many biologically active molecules (see Figure S1 for examples).

Metal-catalyzed intramolecular cyclopropanation of diazo compounds offers a potentially attractive unimolecular approach for stereoselective construction of tricyclic chromanones and chromanes. Among previous reports on both catalytic and thermal processes,[10–13] the intramolecular process has been less developed in comparison with the intermolecular counterpart, let alone with effective control of enantioselectivity. This significant underdevelopment is presumably ascribed to the highly strained transition state associated with existing catalytic systems that typically proceed by concerted mechanisms involving electrophilic metal-locarbene intermediates. To the best of our knowledge, Wood and co-workers reported the only example for stereoselective synthesis of one cyclopropane-fused chromanone derivative in 89% yield with 45% ee through asymmetric intramolecular cyclopropanation using a Rh_2-based catalyst.[12a] In most other cases, the construction of chiral tricyclic chromanones and chromanes with fused cyclopropanes relied on stereoselective intermolecular cyclopropanation of pre-formed

bicyclic structures of chromanones and chromanes. For example, Feng and co-workers reported Ni-catalyzed inter-molecular cyclopropanation of coumarins with phenyliodonium ylide for asymmetric synthesis of two tricyclic chromanones.[12b] Additionally, Sakamoto and co-workers synthesized two enantioenriched cyclopropane-fused chromanones through diastereoselective intermolecular cyclopropanation of prepared chiral coumarins with sulfur ylides.[12c] Furthermore, Zeng and co-workers described asymmetric synthesis of tricyclic chromanones by Lewis base-mediated intermolecular cyclopropanation of coumarin derivatives with 2-bromoacetates.[12d,e] Meanwhile, Yuan, Zhao, and co-workers demonstrated the application of intermolecular cyclopropanation by organocatalysts for asymmetric synthesis of cyclopropane-fused chromanones containing additional spirooxindoles.[12f] More recently, Yang and co-workers employed a chiral organocatalyst for asymmetric synthesis of chromanones through intermolecular reactions of α,β-unsaturated aldehydes with 2,4-dinitrobenzyl chloride.[12g] Although these previous reports disclosed different synthetic approaches, stereoselective construction of cyclopropane-fused chromanones via asymmetric intramolecular cyclopropanation of diazo compounds has been largely undeveloped. There has been even much less development for stereoselective construction of cyclopropane-fused chromanes. In fact, there has been no previous report on catalytic systems for asymmetric intramolecular cyclopropanation of diazo compounds for stereoselective synthesis of tricyclic chromanes containing fused cyclopropanes. Even for asymmetric intermolecular cyclopropanation, only two examples were previously reported.[13] Tang and co-workers demonstrated the synthesis of one chiral tricyclic chromane by Cu-catalyzed intermolecular cyclopropanation of 2*H*-chromene with ethyl α-nitrodiazoacetate.[13a] Recently, Charette and co-workers reported the preparation of another chiral cyclopropane-fused chromane by intermolecular chlorocyclopropanation of a 2*H*-chromene-derived allylic alcohol with dichloromethylzinc carbenoid.[13b] While this manuscript was in the process of submission, Zhuo and co-workers reported an innovative Mo(salen)-based catalytic system for asymmetric synthesis of tricyclic chromanes by deoxygenative intra-molecular cyclopropanation of 1,2-dicarbonyl compounds using tertiary phosphines as the terminal reductants at elevated temperature.[14] As a new application of metalloradical catalysis (MRC), we herein report the development of a Co(II)-based metalloradical system that is highly effective for asymmetric radical bicyclization of both 2-vinylaryl diazomalonates and in situ-generated α-(2-(allyloxy)aryl)diazomethanes. We describe a significant ligand effect on the Co(II)-catalyzed bicyclization process, leading to the identification of two different D_2-symmetric chiral amidoporphyrin ligands for the two catalytic intramolecular cyclopropanation reactions. Supported by the two optimal ligands, the Co(II)-based catalytic system is applicable to wide-ranging diazomalonates and α-aryldiazomethanes, leading to stereoselective construction of cyclopropane-fused tricyclic chromanones and chromanes in high yields with excellent control of both diastereoselectivities and enantioselectivities. Additionally, we present experimental and computational mechanistic studies that offer the insight into the working details of the underlying stepwise radical mechanism for the Co(II)-based catalytic system.

RESULTS AND DISCUSSION

Reaction Development.

Our effort started with the investigation of the radical bicyclization reaction of 2-vinylphenyl diazomalonate **1a** as the model substrate using Co(II)-based metalloradical catalysts (Table 1). It was shown that the simple catalyst [Co(**P1**)] (**P1** = 5,10,15,20-tetraphenylporphyrin) was incapable of activating diazomalonate **1a** as no reaction was observed (Table 1; entry 1). When an achiral metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-IbuPhyrin)[15] was applied, the desired cyclopropane-fused tricyclic chromanone **2a** was observed in 8% yield as the allowed *cis*-ring conjunction (Table 1; entry 2). This encouraging result promoted us to evaluate asymmetric induction during the radical bicyclization with the use of a first-generation chiral metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-ChenPhyrin).[7a] Excitingly, [Co(**P3**)] could enable productive formation of the *cis*-fused tricyclic chromanone **2a** in good yield (50%) with high control of enantioselectivity (89% ee) (Table 1; entry 3). It was noted that the enantioselectivity could be even further enhanced to 96% ee by changing the solvent from toluene to *tert*-butyl methyl ether (Table 1; entry 4). When the catalyst loading was increased to 3 mol %, the catalytic reaction in *tert*-butyl methyl ether delivered *cis*-fused **2a** in high yield (88%) with excellent enantioselectivity (96% ee) (Table 1; entry 5). In view of this positive outcome, we then tested metalloradical catalyst [Co(**P3**)] for potential activation of α-(2-((*E*)-cinnamyloxy)-phenyl)diazomethane **3a′** as the model substrate for asymmetric radical bicyclization. To our delight, [Co(**P3**)] was indeed able to catalyze the radical bicyclization reaction of **3a′** that was in situ generated from sulfonyl hydrazone **3a** in the presence of Cs_2CO_3, delivering the desired cyclopropane-fused tricyclic chromane **4a** in high yield (86%) as the allowed *cis*-ring conjunction with excellent diastereoselectivity (*exo*/ *endo* = 99:1) and promising enantioselectivity (−34% ee) (Table 1; entry 6). When a second-generation metalloradical catalyst [Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-QingPhyrin)[7c] was used, however, *cis*-fused **4a** was formed in a relatively lower yield (80%) with diminished enantioselectivity (23% ee) but still as the sole *exo*-diastereomer (Table 1; entry 7). It is worth mentioning that ligand **P4** differs from ligand **P3** by replacing one of the two methyl groups in **P3** with a phenyl group in each of the four chiral amide units. Interestingly, subsequent use of an analogous chiral metalloradical catalyst [Co(**P5**)] (**P5** = 2,6-DiMeO-QingPhyrin)[16] bearing 2,6-dimethoxyphenyl groups instead of 3,5-di-*tert*-butylphenyl groups as the 5,15-diaryl substituents on the porphyrin ligand gave rise to *cis*-**4a** as the single *exo*-diastereomer in increased yield (90%) with elevated enantioselectivity (42% ee) (Table 1; entry 8). These results signify a positive effect of rigidification in a ligand environment on the control of stereoselectivities for the catalytic radical process. Aiming at further improving the catalytic system, we designed a new metalloradical catalyst [Co(**P6**)] (**P6** = 2,6-DiMe-QingPhyrin) with an even more rigid ligand environment by installing 2,6-dimethylphenyl groups in replacing the 2,6-dimethoxyphenyl groups as the achiral *meso*-aryl units. Gratifyingly, [Co(**P6**)] could catalyze the formation of *cis*-**4a** with dramatically enhanced enantioselectivity (81% ee) without significantly affecting the high diastereoselectivity (*exo*/ *endo* = 96:4) albeit in a much lower yield (56%) (Table 1; entry 9). Delightfully, changing the solvent to trifluorotoluene resulted in considerable improvements in catalytic reactivity

as well as stereoselectivities, affording *cis*-**4a** in 94% yield as the only *exo*-diastereomer with 90% ee (Table 1; entry 10).

Substrate Scope.

Under the optimized catalytic conditions, the scope of asymmetric radical bicyclization by [Co(**P3**)] was evaluated with different 2-vinylaryl diazomalonates **1** as the substrates (Table 2A). Similar to 2-vinylphenyl diazomalonate **1a**, 2-vinylaryl diazomalonates **1b** and **1c**, which contain an electron-donating −OMe substituent at 6- and 4-positions of the aryl group, respectively, were shown to be effective substrates for [Co(**P3**)]-catalyzed radical bicyclization, delivering *cis*-fused tricyclic chromanones **2b** and **2c** in high yields with excellent enantioselectivities (Table 2; entries 2 and 3). The absolute configurations of cyclopropane-fused tricyclic chromanone **2c** was determined as (1*S*,2*S*) by X-ray crystallography. In the same way, 2-vinylaryl diazomalonate **1d** containing a methyl group at the 4-position of the aryl group was demonstrated as a suitable substrate for the radical bicyclization as well, furnishing tricyclic chromanone **2d** in high yield as the *cis*-fused diastereomer with high enantioselectivity (Table 2; entry 4). Additionally, the [Co(**P3**)]-catalyzed asymmetric radical bicyclization could well be applied to 2-vinylaryl diazomalonates with a halogen atom (−F, −Cl, and −Br) at various positions of the aryl group as exemplified for the high-yielding reactions of halogenated diazomalonates **1e**–**1h** to form chromanones **2e**–**2h** as the *cis*-fused diastereomers with high enantioselectivities (Table 2; entries 5–8). Besides monohalogenated substrates, it was found that the Co(II)-based metalloradical system could also effectively catalyze radical bicyclization reactions of dihalogenated 2-vinylaryl diazomalonates **1i**–**1k** bearing the two halogen atoms (−Cl, −Br, and −I) at 4- and 6-positions of the aryl group, affording the corresponding *cis*-fused tricyclic chromanones **2i**–**2k** in good to high yields with high enantioselectivities (Table 2; entries 9–11). In addition to the above diazomalonates **1a**–**1k** containing monosubstituted alkenes, it was found that 2-vinylaryl diazomalonate derivatives bearing 1,2-disubstituted alkenes could also serve as effective substrates for Co(II)-based asymmetric radical bicyclization as demonstrated with the productive reactions of diazomalonates **1l** and **1m** by [Co(**P4**)], generating corresponding *cis*-fused tricyclic chromanones **2l** and **2m** in high yields with varied enantioselectivities (Table 2; entries 12 and 13).

Likewise, the scope of the [Co(**P6**)]-based catalytic system for asymmetric radical bicyclization was examined using different α-(2-(allyloxy)aryl)diazomethanes **3′** in situ generated from the corresponding sulfonyl hydrazones under the optimized conditions (Table 2B). Like α-(2-((*E*)-cinnamyloxy)phenyl)diazomethane **3a′** (Table 2; entry 14), its analogues containing substituents with varied electronic and steric properties on the phenyl group of the cinnamyl unit could be effectively used as metalloradicophiles for the Co(II)-based metalloradical system. For example, α-aryldiazomethanes **3b′** and **3c′** with both electron-donating (−OMe) and electron-withdrawing (−CN) groups could serve as suitable substrates for Co(II)-based asymmetric bicyclization, resulting in the high-yielding formation of chromanes **4b** and **4c** as the allowed *cis*-ring conjunction with both excellent diastereoselectivities and enantioselectivities (Table 2; entries 15 and 16). Similarly, the [Co(**P6**)]-catalyzed radical bicyclization process was applicable to α-aryldiazomethanes **3d′**–**3f′** bearing halogen atoms (−F, −Cl, and −Br), affording

cis-fused tricyclic chromanes **4d**–**4f** in high yields with excellent diastereoselectivities and high enantioselectivities (Table 2; entries 17–19). The absolute configurations of cyclopropane-fused chromanes **4e** and **4f** were determined as (1*S*,2*R*,7*S*) by X-ray crystallography (Table 2; entries 18 and 19). Moreover, the Co(II)-based metalloradical system proved to be similarly effective for asymmetric radical bicyclization of α-(2-((*E*)-cinnamyloxy)aryl)diazomethanes bearing different substituents on the α-aryl group. For example, α-aryldiazomethanes **3g′**–**3j′** with an electron-donating group (−OMe) and halogen atoms (−F, −Cl, and −Br) on the α-aryl rings could be efficiently bicyclized by [Co(**P6**)] to construct *cis*-fused tricyclic chromanes **4g**–**4j** in high yields with excellent diastereoselectivities and good enantioselectivities (Table 2; entries 20–23). Furthermore, this Co(II)-based metalloradical system was shown to be effective for asymmetric radical bicyclization of α-(2-(allyloxy)aryl)diazomethanes containing trisubstituted alkenes as exemplified with the catalytic reaction of α-aryldiazomethane **3k′** by [Co(**P6**)], delivering *cis*-fused tricyclic chromane **4k** in good yield with high control of both diastereoselectivity and enantioselectivity (Table 2; entry 24).Given that the resulting tricyclic cyclopropane-fused chromanones and chromanes occur as common structures in many biologically active molecules, including natural products (Figure S1), we have explored the synthetic application of the Co(II)-based metalloradical system for stereoselective synthesis of target molecules. To this end, we have successfully employed the Co(II)-catalyzed radical bicyclization as a key step for the first asymmetric total synthesis of the natural product (+)-Radulanin J, which was isolated from liverwort *Radula javanica*.[9b] Starting from the commercially available 3,5-dimethoxybenzaldehyde, the relatively complex sulfonyl hydrazone **S8** was synthesized in high yield through a multistep route (Table 2C; see the Supporting Information for details). Excitingly, the in situ-generated α-(2-(allyloxy)-aryl)diazomethane from hydrazone **S8** could be employed as a suitable substrate for catalytic asymmetric radical bicyclization by [Co(**P6**)], leading to the asymmetric construction of (+)-Radulanin J in 51% yield with 43% ee. The synthetic (+)-Radulanin J is both spectroscopically and optically matched with the isolated natural product.[9b] In summary, we have completed the first asymmetric total synthesis of (+)-Radulanin J from 3,5-dimethoxybenzaldehyde through six steps in overall 22% yield with 43% ee (Table 2C; see the Supporting Information for details).

Mechanistic Studies.

Combined experimental and computational studies were performed to shed light on the underlying stepwise radical mechanism of the Co(II)-based metalloradical system for the two bicyclization processes. The density functional theory (DFT) calculations were carried out to elucidate the working details of the catalytic pathways and associated energetics for asymmetric bicyclization of diazomalonate **1a** by the optimal catalyst [Co(**P3**)] (**A**) (Scheme 2A; see the Supporting Information for details). The DFT calculations reveal the binding of diazo compounds **1a** by catalyst **A** through a network of noncovalent attractions, including multiple H-bonds and π-interactions. This binding event, which is exergonic by 15.6 kcal/mol, results in the formation of intermediate **B** in which these noncovalent interactions position the α-carbon atom of **1a** in close proximity to the Co(II)-metalloradical center of catalyst **A** (C···Co: ~2.673 Å) for further activation. The subsequent activation of **1a** by the catalyst [Co(**P3**)], which is exergonic by 5.6 kcal/mol, generates α-Co(III)-malonyl

radical intermediate **C** with the release of dinitrogen as the byproduct. The metalloradical activation, which is associated with a relatively high but accessible energy barrier ($\Delta G_{\mathbf{TS1}}^{\ddagger}$ = 16.1 kcal/mol), is found to be the rate-determining step. According to the DFT calculations, intermediate **C** proceeds facile *6-exo-trig* cyclization through intramolecular radical addition to the C=C bond with a very low activation barrier ($\Delta G_{\mathbf{TS2}}^{\ddagger}$ = 2.5 kcal/mol), which is also exergonic by 12.9 kcal/mol, delivering γ-Co(III)-alkyl radical **D**. As illustrated in the optimized structure of **TS2**, the low barrier is attributed to the multiple attractive H-bonds and π-interactions. By contrast, the alternative pathway of *7-endo-trig* radical cyclization of intermediate **C** is found to have a significantly higher activation barrier ($\Delta G_{\mathbf{TS2'}}^{\ddagger}$ = 7.9 kcal/mol) although the formation of γ-Co(III)-alkyl radical **D′** is even more exergonic ($\Delta G_{\mathbf{D'}}^{0}$ = −22.2 kcal/mol). The large difference in activation barriers between the two intramolecular radical addition pathways is presumably due to the less ring strain of the 6-membered **TS2** associated with *6-exo-trig* radical cyclization than that of the 7-membered **TS2′** associated with *7-endo-trig* radical cyclization. The DFT computations indicate that γ-Co(III)-alkyl radical **D** then undergoes very facile *3-exotet* cyclization through intramolecular radical substitution with an exceedingly low activation barrier ($\Delta G_{\mathbf{TS3}}^{\ddagger}$ = 1.8 kcal/mol), forming cyclopropane-fused tricyclic chromanone **2a** as the final product while regenerating the metalloradical catalyst [Co(**P3**)].

The same type of computational studies was also conducted to examine the catalytic mechanism of asymmetric radical bicyclization of α-aryldiazomethane **3a′** by the optimal catalyst [Co(**P6**)] (**E**) (Scheme 2B; see the Supporting Information for details). The results from the DFT calculations unveil a similar catalytic pathway for the construction of cyclopropane-fused tricyclic chromane **4a** that consists of four fundamental steps involving three key intermediates. First, the binding of diazo compounds **3a′** by catalyst **E** results in the initial formation of intermediate **F**, which is exergonic by 5.5 kcal/ mol. In intermediate **F**, the α-carbon atom of **3a′** is located only 2.262 Å away from the Co(II)-metalloradical center of catalyst **E**. Second, the further activation of the bound diazo compound **3a′** by the catalyst [Co(**P6**)] generates α-Co(III)-benzyl radical intermediate **G**, which is exergonic by 18.6 kcal/ mol. Although it has a relatively low activation barrier ($\Delta G_{\mathbf{TS4}}^{\ddagger}$ = 9.2 kcal/mol), the step of metalloradical activation turns out to be the rate-determining step as the following steps have even lower activation barriers. Third, intermediate **G** proceeds facile *6-exo-trig* cyclization through intramolecular radical addition to the C=C bond with a low activation barrier ($\Delta G_{\mathbf{TS5}}^{\ddagger}$ = 4.0 kcal/mol) to deliver γ-Co(III)-benzyl radical intermediate **H**, which is also highly exergonic by 23.4 kcal/ mol. By comparison, the alternative *7-endo-trig* radical cyclization of intermediate **G** has a much higher activation barrier ($\Delta G_{\mathbf{TS5'}}^{\ddagger}$ = 14.9 kcal/mol), which is endergonic by 2.0 kcal/mol rather than exergonic. Lastly, intermediate **H** undergoes *3-exo-tet* radical cyclization with a relatively low activation barrier ($\Delta G_{\mathbf{TS6}}^{\ddagger}$ = 4.3 kcal/mol) to produce chromane **4a** while regenerating the catalyst [Co(**P6**)]. To investigate the origin of stereoselectivity for asymmetric radical bicyclization of α-aryldiazomethane **3a′** by [Co(**P6**)], the energetic details associated with the generation of corresponding major and minor diastereomers as well as enantiomers were also calculated (Figures S5 and S6; see the Supporting Information for details). The energy profiles are correctly correlated with the observed trends in asymmetric induction and diastereoselectivity. The overall low activation barriers of the two catalytic systems from the DFT calculations are also consistent

with the experimental results that both of the catalytic radical bicyclization processes could proceed effectively at room temperature.

To provide experimental evidence for the existence of the Co-supported organic radical intermediates in the catalytic pathways, the spin trapping reagent *N*-*tert*-butyl-α-phenylnitrone (PBN) and stable radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were employed to trap them for EPR detection and structural characterization, respectively (Scheme 2). We first added the spin trapping reagent PBN into the reaction mixture of diazomalonate **1a** with the catalyst [Co(**P3**)] and then monitored it by X-band electron paramagnetic resonance (EPR) spectroscopy at room temperature (Scheme 2C; see the Supporting Information for details). The observed isotropic EPR spectrum displays the characteristic triplet of doublet signals at the *g*-value of ~2.00, which could be fittingly simulated as two well-defined triplet of doublet signals by involving two PBN-trapped radical species **5** and **6** that are originated from α-Co(III)-malonyl radical $\mathbf{I}_{[\mathrm{Co}(\mathbf{P3})]/\mathbf{1a}}$ and γ-Co(III)-alkyl radical $\mathbf{II}_{[\mathrm{Co}(\mathbf{P3})]/\mathbf{1a}}$ on the basis of the hyperfine couplings by ^{14}N (I = 1) and ^{1}H (I = 1/2): 79% of O-centered radical **5** (g = 2.00632, $A_{(\mathrm{N})}$ = 41.5 MHz,and $A_{(\mathrm{H})}$ = 5.2 MHz) and 21% of O-centered radical **6** (g =2.00645, $A_{(\mathrm{N})}$ = 39.7 MHz, and $A_{(\mathrm{H})}$ = 5.8 MHz). We also added the spin trapping reagent PBN into the reaction mixture of α-aryldiazomethane **3a′** with the catalyst [Co(**P1**)] for EPR detection of the corresponding radical intermediates (Scheme 2D; see the Supporting Information for details). The observed EPR spectrum exhibits strong signals with the distinctive splitting pattern of the triplet of the doublet at the *g*-value of ~2.00. This was taken as the evidence for the formation of a mixture of O-centered radicals **7** and **8** that resulted from PBN trapping of the initially generated α-Co(III)-benzyl radical $\mathbf{III}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{3a}}$ and subsequently formed γ-Co(III)-benzyl radical $\mathbf{IV}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{3a}}$. The observed signals could be agreeably simulated on the basis of hyperfine couplings by ^{14}N (I = 1) and ^{1}H (I = 1/2): 79% of O-centered radical **7** (g = 2.00639, $A_{(\mathrm{N})}$ = 41.1 MHz, and $A_{(\mathrm{H})}$ = 6.7 MHz) and 21% of O-centered radical **8** (g = 2.00649, $A_{(\mathrm{N})}$ = 39.5 MHz, and $A_{(\mathrm{H})}$ = 6.7 MHz). In addition to PBN trapping for EPR detection, significant efforts were made to trap the catalytic radical intermediates by stable radical TEMPO with an aim at isolating the TEMPO-trapped product for structural characterization. After many experimentations, we were excited to be able to successfully isolate a new product **9** in ~7% yield from the reaction mixture of α-aryldiazomethane **3c′** with the catalyst [Co(**P1**)] (2 mol %) in the presence of TEMPO (3.0 equiv) (Scheme 2E). Compound **9** was characterized and further confirmed by X-ray crystallography as a bis-TEMPO-trapped product that contains the two TEMPO units at the α-and γ-positions, respectively. The formation of compound **9** evidently implies the involvement of both the initially generated α-Co(III)-benzyl radical $\mathbf{III}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{3c}}$ and the subsequently formed γ-Co(III)-benzyl radical $\mathbf{IV}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{3c}}$ intermediates. Conceivably, the resulting γ-Co(III)-benzyl radical $\mathbf{IV}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{3c}}$ was trapped by the first molecule of TEMPO through radical recombination to generate intermediate $\mathbf{V}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{3c}}$. The succeeding radical substitution of $\mathbf{V}_{[\mathrm{Co}(\mathbf{P1})]/\mathbf{3c}}$ with another molecule of TEMPO was likely responsible for the final formation of bis-TEMPO-trapped product **9** upon the homolytic cleavage of the weak Co–C bond. The successful trap of γ-Co(III)-benzyl radical **IV** seems in conformity with the finding from the DFT calculations that the radical substitution of intermediate **IV** has a relatively higher activation barrier than the radical addition of intermediate **III** (Scheme 2B). Together, the

results from these experimental and computational studies are taken as convincing evidence in support of the proposed stepwise radical mechanism for Co(II)-based asymmetric radical bicyclization.

CONCLUSIONS

In summary, we have successfully applied Co(II)-based metalloradical catalysis (MRC) for asymmetric radical bicyclization of both stable diazomalonates and in situ-generated α-aryldiazomethanes that contain dangling alkene units to construct valuable tricyclic compounds. We have demonstrated the power and versatility of the D_2-symmetric chiral amidoporphyrin ligand platform in support of the Co(II)-based metalloradical system for molecular construction by homolytic radical chemistry. The key to the success in controlling the stereochemical course of the two new radical processes is the judicious modulation of the D_2-symmetric chiral amidoporphyrin to create a suitable ligand environment that maximizes cooperative noncovalent attractive interactions. With the support of optimized ligands, the Co(II)-based metalloradical system can effectively activate 2-vinylaryl diazomalonates and in situ-generated α-(2-(allyloxy)aryl)-diazomethanes for asymmetric radical bicyclization to construct cyclopropane-fused tricyclic chromanones and chro-manes, respectively, in excellent yields with excellent control of both diastereoselectivities and enantioselectivities for the newly created contiguous stereogenic centers. As a demonstration of synthetic application, the Co(II)-catalyzed radical bicyclization has been employed as a key step for the first asymmetric total synthesis of the natural product (+)-Radulanin J. Our combined computational and experimental studies have suggested that the two catalytic bicyclization processes proceed with a similar stepwise radical mechanism that comprises *6-exo-trig* cyclization of initially generated α-Co(III)-alkyl radicals and *3-exo-tet* cyclization of subsequently formed γ-Co(III)-alkyl radicals. We believe these two Co(II)-based metalloradical systems for asymmetric radical bicyclization will find useful applications in organic synthesis as the resulting chiral chromanones and chromanes are common structures in many biologically active compounds and pharmaceuticals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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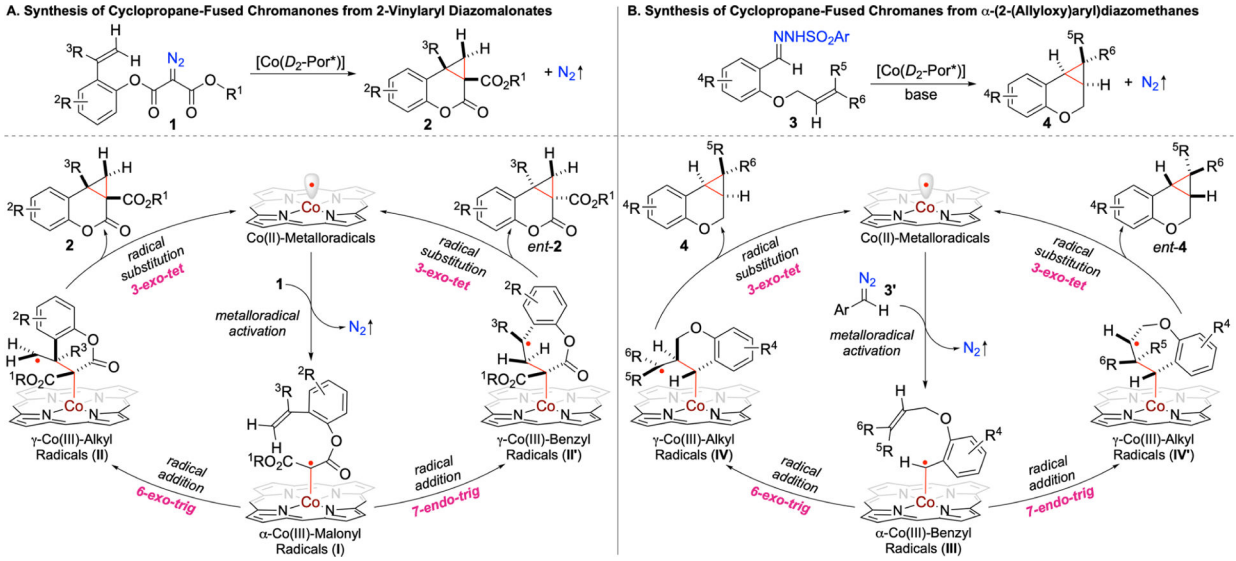
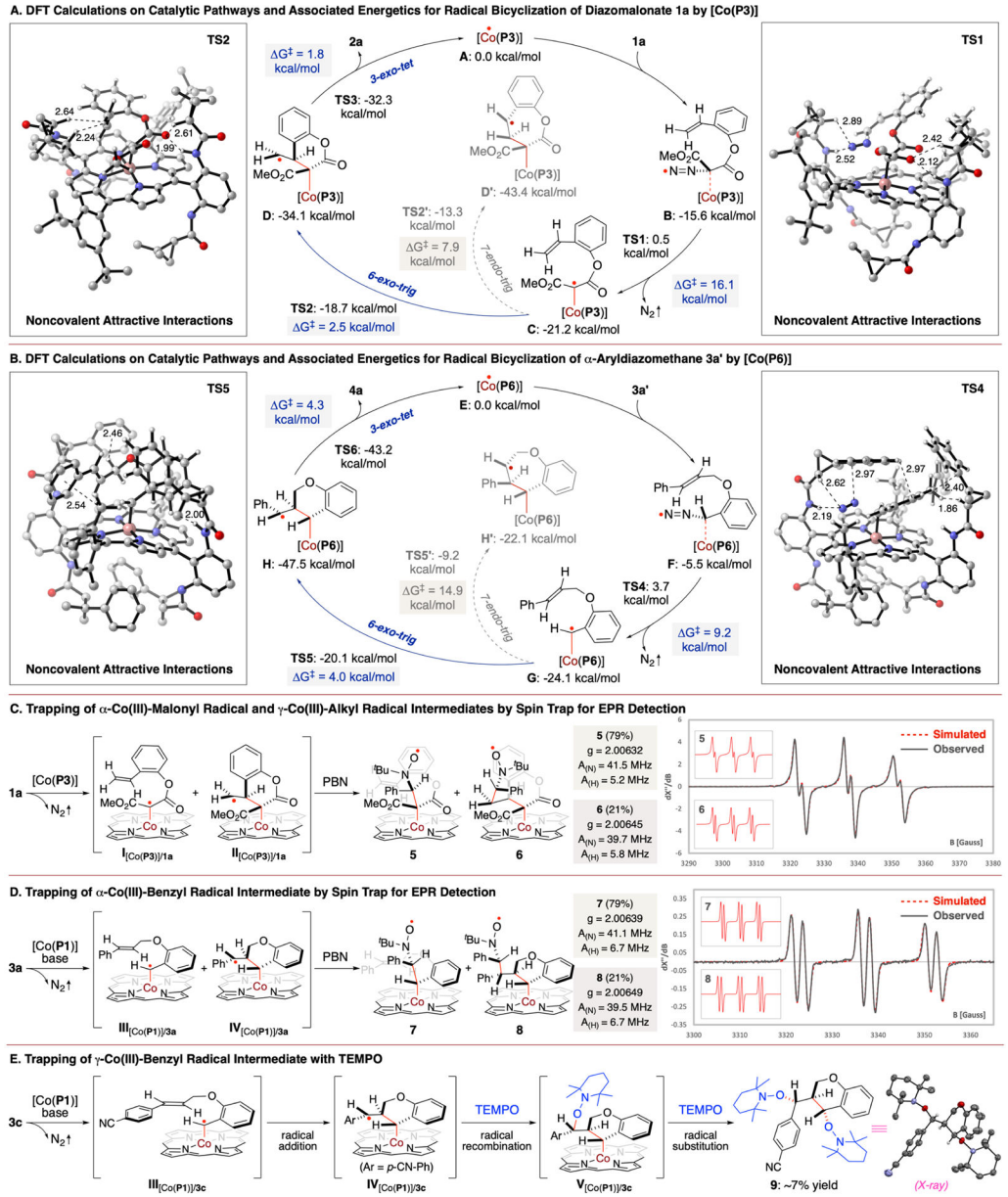


Scheme 1.

Proposal for Stereoselective Construction of Tricyclic Structures through Radical Bicyclization via Co(II)-MRC



Scheme 2.

Mechanistic Studies on Co(II)-Catalyzed Bicyclization Reactions of Diazomalonates and α-Aryldiazomethanes

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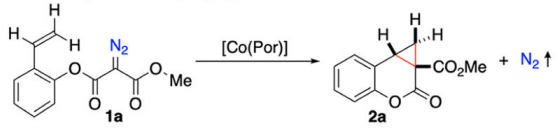
Table 1.

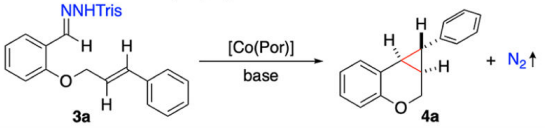
Ligand Effect on Co(II)-Based Catalytic Systems for Asymmetric Radical Bicyclization of Diazo Compounds

A. Stereoselective Synthesis of Cyclopropane-Fused Chromanones[a]

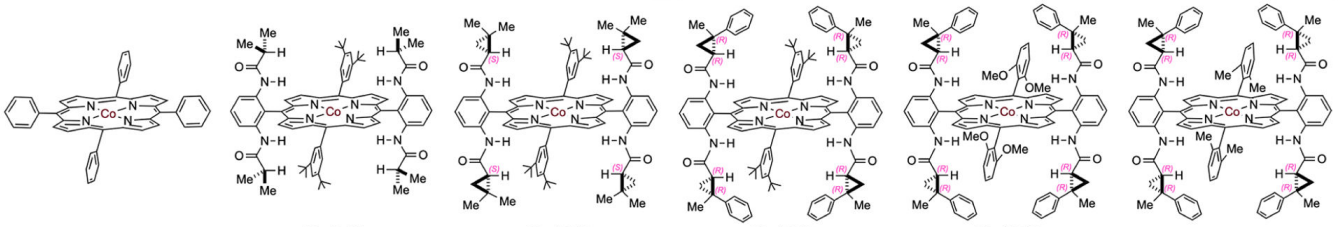


entry	catalyst	solvent	yield (%)[c]	junction	ee (%)[e]
1	[Co(**P1**)]	toluene	0	–	–
2	[Co(**P2**)]	toluene	8	*cis*-fused	–
3	[Co(**P3**)]	toluene	50	*cis*-fused	89
4	[Co(**P3**)]	TBME	62	*cis*-fused	96
5[f]	[Co(**P3**)]	TBME	88	*cis*-fused	96

B. Stereoselective Synthesis of Cyclopropane-Fused Chromanes[b]



entry	catalyst	solvent	yield (%)[c]	*exo*:*endo*[d]	junction	ee (%)[e]
6	[Co(**P3**)]	toluene	86	99:1	*cis*-fused	–34
7	[Co(**P4**)]	toluene	80	99:1	*cis*-fused	23
8	[Co(**P5**)]	toluene	90	99:1	*cis*-fused	42
9	[Co(**P6**)]	toluene	56	96:4	*cis*-fused	81
10	[Co(**P6**)]	trifluorotoluene	94	99:1	*cis*-fused	90



[Co(**P1**)] (**P1** = tetraphenylporphyrin)
[Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-IbuPhyrin)
[Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-ChenPhyrin)
[Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-QingPhyrin)
[Co(**P5**)] (**P5** = 2,6-DiMeO-QingPhyrin)
[Co(**P6**)] (**P6** = 2,6-DiMe-QingPhyrin)

[a] Conducted with **1a** (0.10 mmol) using [Co(Por)] (2 mol %) at room temperature for 24 h.

[b] Conducted with **3a** (0.10 mmol) using [Co(Por)] (2 mol %) in the presence of Cs_2CO_3 (0.20 mmol) at room temperature for 16 h.

[c] Isolated yields.

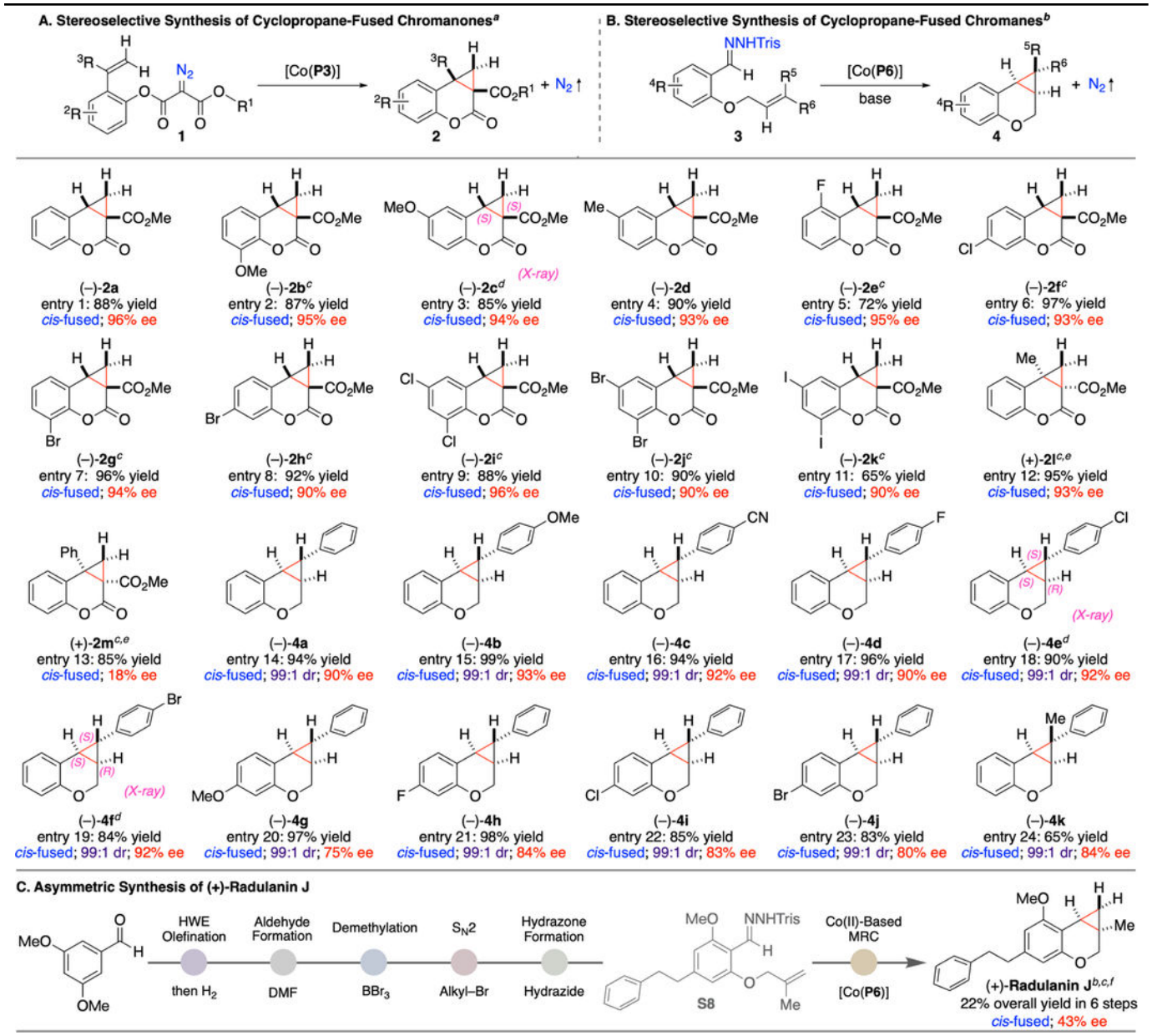
[d] Diastereomeric ratio (dr) between *exo*- and *endo*-isomers determined by ^{1}H NMR analysis of the reaction mixture.

[e] Enantiomeric excess (ee) of major diastereomer determined by chiral HPLC.

[f] Using 3 mol % [Co(Por)]. TBME: *tert*-butyl methyl ether. Tris (trisyl): 2,4,6-triisopropylbenzenesulfonyl.

Table 2.

Scope of Co(II)-Based Catalytic Systems for Asymmetric Radical Bicyclization of Diazo Compounds



J Am Chem Soc. Author manuscript; available in PMC 2024 May 31.

[a] Conducted with **1** (0.10 mmol) using the [Co(**P3**)] catalyst (3 mol %) in *tert*-butyl methyl ether at room temperature for 24 h; isolated yields; only the *cis*-ring junction product formed; enantiomeric excess (ee) of major isomer determined by chiral HPLC.

[b] Conducted with **3** (0.10 mmol) using the [Co(**P6**)] catalyst (2 mol %) in the presence of Cs_2CO_3 (0.20 mmol) in trifluorotoluene at room temperature for 16 h; isolated yields;only the *cis*-ring junction product formed; diastereomeric ratio (dr) between *exo*- and *endo*-isomers determined by ^{1}H NMR analysis of the reaction mixture; enantiomeric excess (ee) of major isomer determined by chiral HPLC.

[c] At 40 °C.

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

[e] Using [Co(**P4**)] (3 mol %).

[f] Using [Co(**P6**)] (4 mol %).