Harnessing Chalcogen-bonding Interactions To Establish Conformational Control in Dirhodium(II) Paddlewheel Complexes

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ABSTRACT: Novel well-defined D_2 -symmetric dirhodium(II) carboxylate complexes that bear axially chiral binaphthothiophene δ -amino acid derivatives have been developed. Conformational control was achieved through chalcogen-bonding interactions between sulfur and oxygen atoms in each ligand, providing well-defined and uniform asymmetric environments around the catalytically active Rh(II) centers. These structural properties render such complexes excellent catalysts for the inside-type asymmetric intramolecular C–H insertion into α -aryl- α -diazoacetates to yield a variety of *cis*- α,β -diaryl γ -lactones, as well as the corresponding *trans*-isomers through epimerization, in high diastereo- and enantioselectivities. Short total syntheses of the naturally occurring γ -lactones cinnamomumolide, cinncassin A₇, and cinnamomulactone were also accomplished using this conformationally controlled catalyst.

INTRODUCTION

Chiral dirhodium(II) paddlewheel complexes are highly valuable catalysts for stereoselective transformations including insertion reactions in X–H bonds (X = C, N, O, *etc.*) (Figure 1A) as well as the stereoselective cyclopropanation of unsaturated C–C bonds through the decomposition of diazo compounds.¹ Some of the most frequently employed chiral dirhodium(II) paddlewheel catalysts are dirhodium(II) carboxylate complexes that bear chiral carboxylate groups as paddlewheel ligands.

The construction of a defined asymmetric environment around the catalytically active center is crucial for the development of potential asymmetric catalysts. However, the construction of defined asymmetric environments can be very difficult, especially in the case of catalysts with rotatable bonds near the catalytically active center. Dirhodium(II) carboxylate complexes represent typical examples of catalysts that suffer from undesirable conformational flexibility around the rotatable C–C bond of the carboxylate groups tethered to Rh(II) (Figure 1B). Their conformational flexibility often complicates the construction of defined chiral environments around the upper (Rh1) and lower (Rh2) rhodium atoms, both of which act as catalytically active centers; however, it also enables the construction of diverse and interchangeable structures with different

molecular symmetry. Specifically, C_{1-} , C_{2-} , C_{4-} , and D_2 -symmetric structures with up-up-up-down, up-up-down-down, all-up, and up-down-up-down ligand arrangements relative to the plane of the rhodium carboxylate moieties, respectively, can be formed (Figure 1B).² The presence of uniform chiral environments around the Rh1 and Rh2 centers is particularly important in C_2 (up-up-down-down)- and D_2 (up-down-up-down)-symmetric catalysts, as inequivalent chiral environments will produce products with non-uniform optical purity. Therefore, an important issue in the development of potential dirhodium(II) carboxylate catalysts is establishing control over the conformational flexibility of the carboxylate ligands around the C–C single bond.

We envisioned that the introduction of an interaction that fixes one conformation of the rotatable carboxylate C–C bond could provide a dirhodium(II) complex with relatively rigid and uniform chiral environments around the Rh1 and Rh2 centers.

We have previously reported the synthesis of axially chiral binaphthyl δ -amino acid (*S*)-**1** and its *N*-protected derivatives (Figure 1C),³ as well as their application as chiral carboxylate ligands in dirhodium(II) carboxylate catalyst **2a** (Figure 2C).⁴ Later, we extended these studies to prepare the binaphthothiophene δ -amino acid (*S*)-**3**, which contains sulfur atoms in its fused π -system, from binaphthothiophene dicarboxylic acid (*S*)-**4** (Figure 1C).^{5,6}

Figure 1. (A) C–X bond insertion reaction catalyzed by a dirhodium(II) carboxylate complex. (B) Conformational flexibility and ligand arrangement in dirhodium(II) carboxylate complexes. (C) Axially chiral binaphthyl and binaphthothiophene δ -amino acids and their chalcogen-bond-containing derivatives. (D) Schematic illustration of the concept for the design of the catalyst used in this study.

Furthermore, racemic **3** was transformed into the corresponding amide derivative **5**.⁶ Single-crystal X-ray diffraction analyses of (*S*)-**4** and **5** revealed chalcogen bonds (S...O interactions) between the oxygen atom of the carbonyl group and the sulfur atom of the naphthothiophene ring, which resulted in a co-planar conformation.

Chalcogen bonding has been recognized as a non-covalent interaction that plays a role in determining the conformation of pharmaceuticals and organic materials.⁷ Recently, this interaction has also received attention as a driving force in organocatalysis⁸ as well as an attractive interaction in supramolecular assembly.⁹ We envisaged that the chalcogen-bonding interactions found in (*S*)-**4** and **5** could be used to lock the conformation of the carboxylate C–C bonds to fix the stereostructure of dirhodium(II) complexes (Figure 1D(a)).¹⁰ Furthermore, this conformational restriction would result in a tilt of the other aromatic ring system of the biaryl ligand toward the inside of the complex to give a narrow and well-defined chiral space near the catalytically active Rh centers (Figure 1D(b)). Such chiral environments can be expected to result in good asymmetric induction.

Asymmetric intramolecular C–H insertion of α -diazoacetates has been investigated as a powerful synthetic tool for constructing a variety of chiral cyclic compounds. These reactions can be classified into two categories based on the type of cyclization that occurs. The first category comprises cyclizations that furnish products in which the ester group is located outside the cyclic system (Figure 2A). In the second category, the ester group is incorporated into the cyclic system as a constituent moiety to afford the corresponding lactone (Figures 2B and 2C). In this paper, these types of cyclizations are referred to as outside- and inside-type cyclizations, respectively.

Although many highly stereoselective outside-type cyclizations have been reported,¹¹ examples of inside-type cyclizations with high enantio- and diastereoselectivities are limited, especially those employing α -aryl- α -diazoester substrates.¹² The highly enantio- and diastereoselective inside-type C–H insertion reaction of **6** to give α,β -diaryl β -lactone **7** has been reported by Davies and co-workers as an exceptional example; however, a trifluoromethyl or halogen group at the *ortho*-position of the α -aryl group was required to ensure satisfactory levels of stereoselectivity.¹³ We have also examined the stereoselective inside-type C–H insertion reaction of 3-butenyl α -aryl- α -diazoacetates **8** catalyzed by **2a** to give α -aryl- β -substituted γ -lactones **9** (Figure 2C).⁴ However, the obtained levels of enantio- and diastereoselectivities were unsatisfactory.

Although this initial attempt using **2a** was unsatisfactory, the asymmetric construction of α -aryl β -substituted γ -lactones continued to attract us, because this type of lactone is frequently found as the core structure of natural products¹⁴ such as cinnamomulide (**13**),¹⁵ cinnassins A₇ (*ent*-**13**),¹⁶ and cinnamomulactone (**14**)¹⁷ (Figure 2D). Therefore, we developed in this study a novel type of dirhodium(II) carboxylate catalyst and revealed that **10**, whose conformation can be controlled via chalcogen-bonding interactions, is a highly valuable catalyst for inside-type intramolecular C–H insertion reactions.

Herein, we report the stereostructures of the sulfur-containing catalyst **10** and related derivatives, together with its successful application in the stereoselective inside-type C–H insertion of **11** to give α,β -diaryl γ -lactones **12**, as well as its extension to the total syntheses of **13**, *ent*-**13**, and **14** (Figure 2D).

Figure 2. Inside- and outside-type asymmetric intramolecular C–H insertion reactions of α -aryl α -diazoesters catalyzed by dirhodium(II) carboxylate complexes.

RESULTS AND DISCUSSION

Preparation and Stereostructure of Dirhodium(II) Carboxylate Complexes

Complex (*S*)-**10**, which bears a trifluoroacetamide group on its binaphthothioiophene framework, was prepared from benzyl ester (*S*)-**15**⁶ by installing a trifluoroacetamide moiety at the aniline-type amino group and successive deprotection of the benzyl group (Scheme 1). Treatment of carboxylic acid (*S*)-**16** with $\text{Rh}_2(\text{OAc})_4$ in

refluxing chlorobenzene led to a smooth ligand exchange from AcOH to (*S*)-**16** on the rhodium(II) centers to afford (*S*)-**10**. We also prepared enantiomer (*R*)-**10**, and the binaphthyl-type **2b**, which contains trifluoroacetamide groups, to compare their catalytic potential to that of **10**.

Scheme 1. Preparation of Biaryl-type Dirhodium(II) Carboxylate Complexes **2b** and (*S*)-**10**.

The success of the catalyst-design concept presented in Figure 1D was confirmed by single-crystal X-ray diffraction analyses of (*S*)-**10** and **2b**. The crystal structure of **2b** is shown in Figure 3A. In the crystalline solid state, **2b** adopts a D_2 -symmetric conformation in which the amide-substituted naphthyl groups reside in an “up-down-up-down” configuration.^{18,19} However, the structure of **2b** was found to be pseudo-symmetric, i.e., the chiral environments around the two rhodium centers (Rh1 and Rh2) are not identical, as indicated by the different geometries of the blue naphthyl groups located at the “up” sides relative to the Rh1 and Rh2 centers (cf. top views from Rh1 and Rh2 in Figure 3A). These inequivalent chiral environments should lead to transition states with different geometry on both Rh centers in the stereo-determining C–C bond-forming step to give a mixture of products with different enantioselectivity. Indeed, **2b** provided only moderate levels of enantioselectivity (67% ee) in the intramolecular C–H insertion of **11a** to give *trans*-lactone **12a** (Table 1, entry 10). Another noteworthy property of **2b** is the hydrogen bond formed between the carboxylate oxygen atom and the amide NH group ($\text{O} \cdots \text{N}$ distance: 2.71(1) Å) in ligand II, which is shown by the dotted line in Figure 3A.

We have previously reported the solid-state stereostructure of the methoxycarbonyl-functionalized binaphthyl-type catalyst **2a** (Figure 3B).⁴ This complex forms a C_2 -symmetric conformation in which the carbamate-substituted naphthyl rings of the ligands are oriented in an “up-up-down-down” conformation. However, this complex also contains unsymmetric chiral environments around Rh1 and Rh2, as shown by the different geometries of the blue naphthyl groups around the Rh1 and Rh2 centers. In this complex, two hydrogen bonds were found between the carboxylate oxygen atoms and the carbamate NH groups of the carboxylate ligands I and II located at the upper side of the complex relative to Rh1 ($\text{O} \cdots \text{N}$ distances: 2.974(7) Å (ligand I); 2.962(7) Å (ligand II); dotted lines in Figure 3B).

Figure 3. (A) Pseudo D_2 -symmetric structure of **2b**. (B) Pseudo C_2 -symmetric structure of **2a**. (C) Twist of the naphthyl rings relative to the π -face of the carboxylate group in **2a** and **2b** expressed as the dihedral angles around the carboxylate C–C bonds of ligands I–IV. In the crystal structures of **2a** and **2b**, the hydrogen atoms and solvent molecules coordinated at the axial positions are omitted for clarity. In the top views of the complexes, the pairs of amide-substituted naphthyl rings located at the upper and lower side relative to the indicated Rh center, are shown in blue and orange, respectively.

This complex also furnished *trans*-**12a** with unsatisfactory levels of enantioselectivity (55% ee) (Table 1, entry 9). This was attributed to the unsymmetric chiral environments around the rhodium centers, similarly to the case of **2b**. The crystal structures suggested that the unsymmetric stereostructures of **2a** and **2b** originate from the irregular angle of the naphthyl rings relative to the π -face of the carboxylate group via the rotation of the carboxylate C–C single bonds, as shown by the variation in their dihedral angles, i.e., ϕ C–C'–C''–O: –13(1)° to 49(1)° for ligands I–IV of complex **2a**, and 13(2)° to –49(1)° for those of complex **2b** (Figure 3C).

On the other hand, in sharp contrast to **2a** and **2b**, complex (*S*)-**10** exhibits a well-ordered D_2 -symmetric stereostructure in which the chiral environments around the Rh1 and Rh2 centers are almost identical (cf. the blue naphthothiophene rings in Figure 4A).^{20,21,22} Unlike in **2a** and **2b**, hydrogen bonding was not observed between the carboxylate oxygen atoms and the amide NH groups of the ligands. Instead, as expected, four chalcogen bonds, one between the sulfur atom of the naphthothiophene ring and the oxygen atom of the carboxylate group of each ligand, were observed in ligands I–IV, and are shown as dotted lines in Figure 4A and exemplified by ligand III in Figure 4B. It should be noted here that all S...O distances (2.84(1)–2.95(1) Å) are shorter than the sum of the van der Waals radii (3.32 Å) of these atoms (Figure 4B). These chalcogen-bonding interactions could restrict the flexibility around the carboxylate C–C bonds, thus resulting in a co-planar alignment of the carboxylate groups and the naphthothiophene π -systems in all the ligands (ϕ S–C–C–O $\leq \pm 16(2)^\circ$) (Figure 4B). The defined conformations of the carboxylate moieties are crucial for the nearly perfect symmetric structure of **10**. Moreover, as expected, the co-planar geometry of the carboxylate and the naphthothiophene π -systems force the alternating naphthothiophene rings (blue) to tilt towards the Rh centers (cf. side view of the complex in Figure 4C). Due to the tilted aromatic rings in this D_2 -symmetric arrangement, trapezoidal chiral spaces are formed near each Rh center (the chiral space around Rh2 is indicated by a dotted line).

Furthermore, chalcogen bonds between the carbonyl oxygen atom of the trifluoroacetamide moiety and a sulfur atom are also observed in all these ligands (S'...O' distances: 2.82(2)–2.97(2) Å) (Figure 4B). These chalcogen-bonding interactions cause the trifluoroacetamide moieties to form a five-membered 'heterocycle' parallel to the naphthothiophene rings (Figure 4B). The space-filling model of **10** revealed that a wide chiral cleft is formed by the fused cyclic systems of the naphthothiophene and trifluoroacetamide moieties (Figure 4D). Having successfully achieved promising symmetry and defined structural properties for asymmetric induction, we then moved to examine inside-type intramolecular C–H insertion reactions using complex **10**.

Inside-type Intramolecular C–H Insertion Reactions and Total Synthesis of Natural Products

The potential for asymmetric induction of each Rh complex was evaluated in the intramolecular C–H insertion reaction of **11a**, as the product of this reaction provides ready access to cinnamomulide (**13**) (Table 1).

After finding appropriate conditions by screening solvents and temperature (for details, see the SI), the intramolecular C–H

Figure 4. (A) D_2 -symmetric structure of (*S*)-**10**. Hydrogen atoms and solvent molecules coordinated at the axial positions are omitted for clarity. In the top views of **10**, the pairs of amide-substituted naphthothiophene rings located at the upper and lower side relative to the indicated Rh centers are shown in blue and orange, respectively. (B) Dihedral angles of S-C-C-O and S'-C'-N'-C'', as well as the S...O and S'...O' distances of each ligand; the locations of these angles and distances are illustrated using ligand III. (C) Side view of **10**. The blue amide-substituted naphthothiophene rings are located on the Rh(2) side. (D) Space-filling model of the top view from Rh(2).

insertion was examined in the presence of 2.0 mol% of the dirhodium(II) carboxylate complex in refluxing CH_2Cl_2 . In all cases, *cis*-**12a** was obtained as the initial product in perfect diastereoselectivity (*cis* : *trans* > 99 : 1). However, although *cis*-**12a** was isolable, isomerization of *cis*-**12a** to *trans*-**12a** was sometimes observed during the isolation. Therefore, epimerization to *trans*-**12a** was carried out by treatment with DBU after work up of the C-H insertion reaction. The chemical yield of *cis*-**12a** was determined using an internal standard, and the asymmetric induction was evaluated using the enantiomeric excess (ee) of *trans*-**12a**. The same ee value (95% ee) was measured for the isolated *cis*-**12a** and *trans*-**12a**, demonstrating that no change in the optical purity occurred during the epimerization (entry 11 vs. 12).

Initial trials of this reaction using several established catalysts, including $\text{Rh}_2(\text{S-DOSP})_4$,²³ $\text{Rh}_2(\text{S-PTTL})_4$,²⁴ $\text{Rh}_2(\text{R-TCPTTL})_4$,²⁵ $\text{Rh}_2(\text{S-PTAD})_4$,^{11c} $\text{Rh}_2(\text{S-NTTL})_4$,²⁶ $\text{Rh}_2(\text{S-BTPCP})_4$,²⁷ and $\text{Rh}_2(\text{S-R-MEPY})_4$,²⁸ resulted in only low to medium levels of enantioselectivity (Table 1, entries 1–7). Moreover **2a**, **2b**, and binaphthyl-type catalyst **17**²⁹ were also tested. The use of **17** did not improve the ee (29%; entry 8). On the other hand, the pseudo C_2 -symmetric catalyst **2a** (Figure 3B) furnished *trans*-**12a** in 55% ee (entry 9), while pseudo D_2 -symmetric **2b** (Figure 3A) further improved the enantioselectivity to give *trans*-**12a** in 84% yield with 67% ee (entry 10). Although the stereoselectivity was still unsatisfactory, some improvement was observed using binaphthyl-type catalysts **2a** and **2b** instead of **17** (entries 9 and 10 vs. entry 8). While the different symmetry of the Rh complexes should significantly affect their performance with respect to enantioselectivity, the hydrogen bond formed between the carboxylate oxygen atom and the NH group of the amide and the carbamate substituents in **2a** and **2b** might also contribute to their increased stereoselectivity by acting as a conformational lock. A plausible explanation for the limited enantioselectivity of **2a** and **2b** might be the inequivalent chiral environments around their rhodium centers (Rh(1) and Rh(2)) (Figs. 3A and 3B). These inequivalent chiral environments might lead to a decrease in enantioselectivity through transition states with different geometry in the stereo-determining C-C-bond-forming step. Thus, we examined the binaphthothiophene catalyst **10**.

As expected, the stereoselectivity was dramatically improved by the trifluoroacetamide-bearing (*R*)-**10**, which gave *trans*-**12a** in 95% yield with 95% ee (entry 11). The initial product of the C-H insertion, *cis*-**12a**, was isolated in 95% yield with 95% ee under the same conditions (entry 12). These results confirm that **10** is valuable for preparing both the corresponding *cis*- and *trans*-isomers in high diastereo- and enantioselectivity. As described below, the absolute configuration of *trans*-**12a** was determined as 3*S*,4*S* by comparison of its optical rotation after transformation into cinnamomumolide (**13**).

The remarkable improvement in enantioselectivity using **10** corroborates the importance of conformational control of the paddlewheel catalyst to give uniform and defined chiral environments around the catalytically active centers. This improvement further highlights the value of the conformational control of ligands through chalcogen-bonding interactions. Furthermore, not only the stereoselectivity, but also the chemical yield of the product improved when **10** was used. In this reaction, the dimerization of substrate **11a** tends to compete with the intramolecular C-H insertion to generate side products.³⁰ The well-defined and rigid pockets formed by the

Table 1. Survey of Dirhodium(II) Carboxylate Catalysts Tested in the Asymmetric Intramolecular C–H Insertion of **11a.^a**

entry	Rh catalyst	<i>cis</i> - 12a (%) ^b	<i>trans</i> - 12a (%) ^c	ee (%) ^d of <i>trans</i> - 12a
1	Rh ₂ (<i>S</i> -DOSPP) ₄	71	68	27
2	Rh ₂ (<i>S</i> -PTTL) ₄	64	64	−41
3	Rh ₂ (<i>S</i> -TCPTTL) ₄	80	80	−37
4	Rh ₂ (<i>S</i> -PTAD) ₄	61	60	−39
5	Rh ₂ (<i>S</i> -NTTL) ₄	69	68	−54
6	Rh ₂ (<i>R</i> -BTPCP) ₄	97	96	40
7	Rh ₂ (<i>5R</i> -MEPY) ₄ ^e	41	20	47
8	17	83	85	29
9	2a	65	60	55
10	2b	84	84	67
11	(<i>R</i>)- 10	96	95 ^f	95
12	(<i>R</i>)- 10	95 ^f (95% ee) ^g

^aStandard reaction conditions: **11a** (33.5 mg, 0.075 mmol, 1.0 equiv.) in degassed CH₂Cl₂ (0.75 mL) was added over 1.5 h to 4.5 mL of a refluxing CH₂Cl₂ solution of the dirhodium(II) catalyst (1.5 μmol, 2.0 mol%); then, refluxing was continued for 1 h. ^bDetermined by integrating the ¹H NMR signals in the presence of the internal standard 1,3,5-trimethoxybenzene. ^cNMR yield over two steps. ^dDetermined by chiral HPLC analysis. ^e5 mol% of Rh₂(*5R*-MEPY)₄ was used. ^fIsolated yield. ^gEe (%) of isolated *cis*-**12a**.

naphthothiophene rings around the Rh centers of **10** might also help to prevent these side reactions.

Having achieved satisfactory results using **10**, we then explored its substrate scope. First, we tested substrates with a variety of α-aryl groups (Table 2A). The reactions of unsubstituted **11b** and of **11c**–**11e**, which contain halogen groups at the *para*- or *meta*-positions,

gave the corresponding products (*cis*- and *trans*-**12b**–**12e**) in good yield with excellent enantioselectivity (90–95% ee). The presence of a *t*-Bu group at the *para*-position of **11f** was still acceptable. On the other hand, a remarkable decrease in the chemical yield was observed in the reactions of *para*-methoxy-substituted **11g**, with 34% yield of the *trans*-isomer, although the enantioselectivity remained high. This could be due to the decreased electrophilicity of the rhodium-carbenoid intermediate formed by the α-phenyl moiety with an electron-donating *para*-methoxy group. In contrast, **11h**, which contains two methoxy groups at its *meta*-positions, afforded *cis*-**12h** in high yield and 93% ee. The electron-withdrawing inductive effect of the *meta*-substituted methoxy groups may have contributed to this high yield. Naphthyl groups were also accepted and furnished *cis*- and *trans*-**12i** and **12j** in excellent yield, whereby **12j** showed the highest enantioselectivity of all products (96% ee). The absolute configuration of *trans*-**12b** (3*S*,4*S*) was determined by comparison of its optical rotation to literature values³¹ (cf. SI), and the absolute configuration of the other products was assigned in analogy.

Subsequently, we tested the effect of the ester moiety (Table 2B). The reactions of the tested substrates generally proceeded with high enantioselectivity (87%–93% ee for *trans*-**12k**–**12r**), although their chemical yield varies depending on the electronic nature of the aromatic rings. While the methoxy-functionalized substrates **11o** and **11p** afforded the products in excellent yield, substrates **11k**–**11n**, which bear electron-withdrawing groups, furnished the corresponding γ-lactones in moderate yield. This may have been due to the poorer stabilization of the positive charge at the benzylic position generated in the transition state for C–H insertion. Unfortunately, the C–H insertion of thiophene derivative **11s** and our previous substrate **8** did not produce promising results, providing the corresponding products *trans*-**12s** and *trans*-**9** in 46% yield and 77% ee as well as 26% yield and 75% ee, respectively.

Substrates bearing bromo, alkoxy, or 2-naphthyl groups on the α-aryl groups and electron-abundant aromatic groups in ester moieties generally furnished the corresponding products in high yield and enantioselectivity (Table 2C). It is noteworthy that substrate **11t** was reasonably converted on the gram scale at a reduced catalyst loading (0.5 mol%) to give *trans*-**12t** in 90% yield and 93% ee (cf. dashed box). In the case of **12u** and **12v**, the *cis*-γ-lactones were isolated to demonstrate the utility of this reaction for producing the *cis*-isomer.

Having established the substrate scope, we then applied the reaction to the total syntheses of naturally occurring γ-lactones. Cinnamomulide (**13**), which exhibits a 3*S*,4*S* configuration, and its enantiomer, cinnassin A₇ (*ent*-**13**), which exhibits a 3*R*,4*R* configuration, were readily prepared by removal of the benzyl group of the enantiomers *trans*-**12a** and *ent*-*trans*-**12a** (Scheme 2). Substrate **11a** was prepared from the commercially available compounds **18** and **19** in two steps. Therefore, cat. **10** enables the five-step stereoselective total syntheses of **13** and *ent*-**13** in 59% and 51% total yield, respectively. The absolute configurations of the prepared compounds were confirmed by comparison of their optical rotation with literature values.^{15b,16} Furthermore, the total synthesis of cinnamomulactone (**14**) was achieved in five steps via the asymmetric intramolecular C–H insertion of **11z**, which was prepared from commercially available **20** and **21**, in the presence of (*S*)-**10**, followed by deprotection of the benzyl groups of **12z** (Scheme 3). Compound **14** was synthesized in the naturally occurring form, given that the optical rotation of

Table 2. Intramolecular C–H Insertion to Give a Variety of *Cis*- and *Trans*- γ -lactones.^a

^aStandard reaction conditions: **11** (0.075 mmol, 1.0 equiv.) in degassed CH₂Cl₂ (0.75 mL) was added over 1.5 h to 4.5 mL of a refluxing CH₂Cl₂ solution of **10** (3.43 mg, 1.5 μ mol, 2.0 mol%); then, refluxing was continued for 1 h. ^bDetermined by integrating the ¹H NMR signals in the presence of the internal standard 1,3,5-trimethoxybenzene, except in the cases of **12u** and **12v**. ^cDetermined by chiral HPLC analysis. ^dCatalyst (*S*)-**10** was used.

synthesized **14** had the same sign as the isolated one from natural source.¹⁷ However, the absolute configuration of **14** has not yet been determined, although the 3*R*,4*R* configuration was elucidated based on the opposite sign of the optical rotation ($[\alpha]_D^{25} = -193$ in CH₂Cl₂) relative to that of cinnamomumolide (**13**) ($[\alpha]_D^{25} = +161.5$

in CH₂Cl₂).¹⁷ To determine the absolute configuration of **14** unambiguously, the CD spectra of synthesized cinnamomumolide (3*S*,4*S*)-**13**, cinnacassin A₇ (3*R*,4*R*)-*ent*-**13**, and **14** were compared (Figure S). Both **14** and *ent*-**13** show negative Cotton effects at

Scheme 2. Asymmetric Syntheses of Cinnamommumolide (13**) and Its Enantiomer Cinnacassin A7 (*ent*-**13**).**

Scheme 3. Asymmetric Synthesis of Cinnamumulactone (14**).**

Figure 5. CD and UV spectra of **13**, *ent*-**13**, and **14** in MeOH.

270–300 nm, 230–250 nm, and 200–220 nm, which clearly indicates a 3*R*,4*R*-configuration of **14**. The mirror image pattern of the CD spectra for **14** and (3*S*,4*S*)-**13** also support the 3*R*,4*R*-configuration of **14**. These asymmetric total syntheses aptly demonstrate the high applicability of **10** for the preparation of optically active α,β -diaryl γ -lactones.

CONCLUSIONS

Chiral dirhodium(II) carboxylate complex **10**, which is conformationally controlled via chalcogen-bonding interactions, was developed. A single-crystal X-ray diffraction analysis indicated that the Rh centers in **10** are embedded in uniform and defined chiral environments that arise from the presence of intramolecular chalcogen bonds. **10** demonstrated outstanding catalytic performance in diastereo- and enantioselective inside-type intramolecular C–H insertion reactions, as well as versatile synthetic utility in the concise asymmetric syntheses of the naturally occurring α,β -disubstituted γ -lactones such as **13**, *ent*-**13**, and **14**. These results demonstrate the importance of establishing conformational control in chiral paddle-wheel complexes in order to achieve remarkable asymmetric induction. Furthermore, these results highlight the effectiveness of a non-covalent interaction in controlling the conformation of catalysts that bear a rotatable bond near the catalytically active center. Further examination and applications of this concept of establishing conformational control via chalcogen bonding in asymmetric catalysts are currently in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectroscopic data for all new compounds (PDF).

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(22) It is noteworthy that the molecular symmetry changes from C_2 to D_2 from **2a** to **2b** and **10**. At present, we do not have a clear explanation for this change in symmetry. However, in the cases of **2b** and **10**, close contacts between the fluorine atoms of the trifluoroacetamide groups on different ligands were observed (cf. SI). These contacts might also act as conformational locks in the D_2 -symmetric structures. An example of fluorine-fluorine close contact, see: Rusek, M.; Kwasna, K.; Budzianowski, A.; Katrusiak, A. Fluorine...Fluorine Interactions in a High-Pressure Layered Phase of Perfluorobenzene. *J. Phys. Chem. C* **2020**, *124*, 99–106.

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