

Letter

## Cobalt(II)-Salen-Linked Complementary Double-Stranded Helical Catalysts for Asymmetric Nitro-Aldol Reaction

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# **Cobalt(II)-Salen-Linked Complementary Double-Stranded Helical Catalysts for Asymmetric Nitro-Aldol Reaction**

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**ABSTRACT:** Double-helical, bimetallic chiral Co(II)-salen complexes stabilized by chiral amidinium–carboxylate salt bridges efficiently catalyzed the asymmetric nitro-aldol (Henry) reaction, producing products with up to an 89% enantiomeric excess (ee); the reactivity and enantioselectivity were higher than those catalyzed by the corresponding single strands. The key role of the chiral double-helical framework for the supramolecular bimetallic catalysis has been revealed by a double-helical catalyst carrying achiral Co(II)-salen units that promoted the Henry reaction, yielding the product with a 50-45% ee, while the corresponding single strands showed a poor or no enantioselectivity.

The helix is inherently chiral and is one of the key structural motifs for biological systems in which single-stranded helical peptides and double-helical nucleic acids with a one-handed helicity play a central role in their vital functions. In the organic, polymer, and supramolecular chemistry fields, a vast number of helical molecules, oligomers (foldamers), and polymers has been synthesized, primary to mimicking biological helices, and also to develop chiral materials with specific functionalities that involve chiral recognition and sensing, asymmetric catalysis, and chiral optoelectronic properties.<sup>1</sup> However, most of synthetic helical systems are composed of single-stranded helices, while those of the double helices with defined structures remain limited to peptide nucleic acids (PNA),<sup>2</sup> helicates,<sup>3</sup> and aromatic oligoamides.<sup>4</sup> Moreover, synthetic double helices showing an asymmetric catalytic activity are quite rare,<sup>5</sup> regardless of the recent finding that the doublehelical DNA catalyzes a variety of reactions in a highly enantioselective fashion when complexed with specific metalcoordinated ligands,<sup>6</sup> which indicate the potential capability of double helices as a promising chiral framework for supramolecular asymmetric catalysis.

It was recently demonstrated by Hong and co-workers<sup>8</sup> that an optically-active Co(II)-salen complex bearing selfcomplementary 2-pyridone and 2-amidopyridine units on each side of the complex self-assembled to form a dinuclear zipperlike homo-duplex through relatively weak interstrand hydrogen-bonding. The bimetallic Co(II)-salen duplex<sup>9</sup> efficiently catalyzed the asymmetric nitro-aldol (Henry) reaction<sup>10</sup> with a remarkable enhancement of the catalytic activity as well as the enantioselectivity compared to those catalyzed by the monomeric Co(II)-salen complex. We anticipated that if such a selfassembled dinuclear complex could take a one-handed doublehelical structure, the resulting supramolecular bimetallic double-helical catalyst would enhance the enantioselectivity and catalytic activity due to its intriguing synergistic effect of the helical chirality and cooperative effect of the two metal units arranging in close proximity to one another in a chiral fashion (Figure 1).



**Figure 1.** Complementary double-helix formation between chiral and/or achiral Co(II)-salen-linked carboxylic acid dimers and amidine dimers stabilized by chiral amidinium–carboxylate salt bridges that enhance or induce the enantioselectivity during the asymmetric Henry reaction due to their one-handed double-helical framework.

We now describe a proof-of-concept example of a doublehelical framework for supramolecular bimetallic catalysis and demonstrate control over the reaction yield and enantioselectivity that are significantly enhanced upon the one-handed double-helix formation of chiral and/or achiral complementary single strands carrying catalytically-active chiral and even achiral metal species.

Our design strategy for constructing double-helical bimetallic catalysts is based on our modular strategy developed for constructing *m*-terphenyl-based complementary double helices stabilized by chiral amidinium–carboxylate salt bridges<sup>5a,11</sup> that have a high stability with association constants  $>10^7$  M<sup>-1</sup> in

CHCl<sub>3</sub> and a tolerance to various functional groups and metals,<sup>11b,d</sup> which provides a key advantage such that a variety of linkers including metals can be introduced to the linkages while maintaining the double-helical structures with a controlled handedness biased by the chiral amidine residues.<sup>11</sup>

Chart 1. Structures of Chiral Amidine and Carboxylic Acid Dimer Strands Connected through Chiral or Achiral Salen and Metal-Salen Linkers



We then synthesized a series of (R)-1-phenylethyl amidine (a) and its complementary carboxylic acid (c) dimers with an *m*-terphenyl backbone joined by chiral Ni(II)- (L2; 2a, 2c), chiral Co(II)- (L3; 3a, 3c), and achiral Co(II)-salen (L5; 5a, 5c) linkers, respectively (Chart 1). These dimer strands were prepared from the corresponding metal-free dimers (L1 and L4; 1a, 1c, 4a, 4c) by metalation with nickel acetate or cobalt acetate.<sup>12</sup>

The duplex formations of a series of the complementary dimer strands prepared by mixing a 1:1 molar ratio were con-

firmed by electron-spray ionization mass spectrometry (ESI-MS) (Figure S1). A double-helix formation was further investigated in detail by measuring the 1D and 2D <sup>1</sup>H NMR spectroscopies of the chiral Ni(II)-salen-linked 2a 2c complex in CDCl<sub>3</sub>. The salt-bridged N-H protons showed two sets of nonequivalent signals around  $\delta = 13.3$  ppm (Figure S2) and several NOE cross-peaks were clearly observed between the dimer strands in the 2D NOESY spectrum (Figures S4 and S5), which is indicative of the double-helix formation stabilized by salt bridges as observed for other analogous complementary double helices.<sup>11d</sup> An excess single-handed double-helical structure was supported by the circular dichroism (CD) spectrum of the 2a 2c complex in CDCl<sub>3</sub> (Figure 2a); an intense split-type Cotton effect appeared, especially in the absorption region of the conjugated linkages (ca. 300-420 nm), whereas the single strands 2a and 2c exhibited weak CD signals in the same region, suggesting that the  $2a \cdot 2c$  likely adopts a righthanded double-helical structure whose helical sense is controlled by the chiral amidine residues with an (R)configuration.<sup>11</sup>

Other duplexes composed of chiral and/or achiral Co(II)and/or Ni(II)-salen-linked amidine and carboxylic acid dimers also exhibited more intense Cotton effects than those of the corresponding single strands in the linker chromophore regions, and the CD spectral patterns and signs of these duplexes were almost comparable to each other (Figures 2 and S7), indicating that these dimers most likely adopt a double-helical structure with the same helical sense when hybridized with their complementary strands, although their CD intensities were more or less different from each other due to the difference in their linker salen chirality and metal species (Ni or Co).<sup>13</sup>

Interestingly, the 5a 5c duplex joined by achiral Co(II)-salen



Figure 2. (a-c) CD and absorption spectra of 2a, 2c, and 2a·2c (a), 3a, 3c, and 3a·3c (b), and 5a, 5c, and 5a·5c (c) in CDCl<sub>3</sub> at 25 °C (0.50 mM). (d and e) The energy-minimized complementary double-helical structures of chiral Ni(II)-salen-linked 2a·2c (d) and achiral Ni(II)-salen-linked 5a'·5c' (e) obtained by the semiempirical molecular orbital calculations (see Figure S6) which indicate that the two metal-salens with *anti*-geometry are arranged in a left-handed twist manner with a Ni–Ni distance of 4.90 and 5.01 Å for 2a·2c and 5a'·5c', respectively, and each salen unit possesses one of the enantiomerically-twisted conformations induced by the chirality of the salen (2a·2c) and a one-handed double-helical framework of 5a'·5c'.

## **ACS Paragon Plus Environment**

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59 60 linkers showed a relatively intense Cotton effect in the linkage chromophore region (Figure 2c), resulting from the amidine chirality of **5a** that induces a preferred-handed double-helical structure when complexed with the totally achiral complementary **5c**, thus further inducing one of the enantiomeric twisted conformations of both achiral Co(II)-salen units (Figure 2e and see below). The double helices (**2a** · **2c**, **3a** · **3c**, and **5a** · **5c**) were stable in CDCl<sub>3</sub> and showed negligible changes in their CD spectra within the temperature range from 50 to -10 °C (Figure S8). The association constants for the double-helix formations between **2a** and **2c**, and **3a** and **3c** at 25 °C in CDCl<sub>3</sub> were estimated to be ca.  $8.2 \times 10^{11}$  and  $> 1.8 \times 10^{9}$  M<sup>-1</sup> based on the competition <sup>1</sup>H NMR titration (Figures S9 and S10)<sup>11d</sup> and CD dilution experiments (Figure S11), respectively.

With this structural information in hand, the catalytic activity and enantioselectivity of the chiral and/or achiral bimetallic Co/Co- and Co/Ni-salen-linked complementary double helices were investigated regarding the asymmetric Henry reaction of 4-nitrobenzaldehyde (7) with nitromethane in  $CH_2Cl_2$  at -30 °C (Table 1).<sup>14</sup> For comparison, the corresponding Co(II)salen-linked dimers along with the model Co(II)-salen complex  $6_{C_0}$  were also used as the catalysts. Interestingly, the chiral bimetallic Co(II)-salen-linked double-helix 3a·3c efficiently catalyzed the Henry reaction to produce the nitromethyl adduct (8) in 91% yield with the excellent enantioselectivity of 89% ee ((S)-rich) (entry 4),<sup>15</sup> whereas the corresponding amidine dimer catalyst 3a afforded the product in good yield (67%), but with a modest enantioselectivity (55% ee) being comparable to that catalyzed by  $6_{C0}$  (56% ee) (entries 1 and 13).

The carboxylic acid dimer **3c** produced **8** with a relatively higher ee (74%) than **3a** and model **6**<sub>C0</sub>, although the product yield was low  $(12\%)^{16}$  (entry 2) because **3c** was not soluble in CH<sub>2</sub>Cl<sub>2</sub> and used in the dispersed state.<sup>17</sup>

In order to obtain more convincing evidence for the cooperative catalytic and enantioselective activities assisted by the Co/Co-bimetallic salen catalysts during the Henry reaction,<sup>10</sup> one of the chiral Co(II)-salen linkers of **3a**·**3c** was replaced by the catalytically-inactive chiral Ni(II)-salen linker. The Co/Nibimetallic catalysts (**3a**·**2c** and **2a**·**3c**) afforded the product **8** in much lower yields (27 and 20%) accompanied by a decrease in the enantioselectivity (60 and 40% ee, respectively) (entries 5 and 6), demonstrating the important role of the chiral Co/Co-bimetallic salen-linked double-helical nature of **3a**·**3c** on the reaction yield and enantioselectivity for the present Henry reaction.

A key role of the chiral double-helical framework for supramolecular bimetallic catalysis has been further unambiguously revealed by the achiral Co/Co-bimetallic salen-linked double-helical catalyst **5a 5c** that promoted the Henry reaction with an encouraging enantioselectivity, yielding the product **8** with a 50-45% ee (entries 11 and 12), while the corresponding single strands **5a** and **5c** showed a poor (5% ee) and no enantioselectivity, respectively (entries 9 and 10), although the yield was low (6-13%) due to the poor solubility of the catalyst **5a 5c** in CH<sub>2</sub>Cl<sub>2</sub> (1.46 mM). The energy-minimized structures of the right-handed double helices joined by the chiral (**2a 2c**) and achiral (**5a**' **5c**') Ni(II)-salen linkers (Figures 2d, e and S6) suggest that the two chiral amidinium–carboxylate salt bridges enabled the two strands to be held together, thus intertwining into the right-handed double-helical structure<sup>11a,d</sup> and

Table1.AsymmetricHenryReactionofo-MethoxybenzaldehydeCatalyzedby a Series ofCo(II)-SalenDimers and ComplementaryDouble Helices<sup>a</sup>

MeO	СНО + 7 +	CH <sub>3</sub> NO <sub>2</sub> 10 equiv.	Co- DIPEA CH <sub>2</sub> CI	-salen (2 mol%) (2 mol%) ₂, −30 °C	MeO OH	NO <sub>2</sub>
entry	catalyst (Co(II) -salen)	Co(II)- salen (mol%)	time (h)	conversion <sup>b</sup> (%)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>3</b> a	2	90	86	67	55
$2^d$	3c	2	90	96	12	74
3 <sup>e</sup>	3c	2	90	98	1	55
4	3a-3c	4	90	93	91	89
5	3a·2c	4	90	99	27	60
6	2a·3c	4	90	92	20	40
7	3a·5c	4	90	95	70	66
8	5a·3c	4	90	96	87	74
9	5a	2	90	96	38	5
10	5c	2	90	94	16	0
$11^{f}$	5a · 5c	4	115	11	6	50
12 <sup>f</sup>	5a·5c	4	235	23	13	45
13	6 <sub>Co</sub>	2	90	94	17	56
$14^e$	<b>6</b> <sub>Co</sub>	2	90	98	1	53

<sup>*a*</sup> The reaction was carried out in CH<sub>2</sub>Cl<sub>2</sub> or THF at -30 °C. [catalyst] = 24.8 mM. <sup>*b*</sup> Conversion and yield were estimated by <sup>1</sup>H NMR. <sup>*c*</sup> Ee values ((*S*)-rich) were determined by chiral HPLC. <sup>*d*</sup> Dispersed in CH<sub>2</sub>Cl<sub>2</sub>. <sup>*e*</sup> In THF. <sup>*f*</sup> [**5a** •**5c**] = 1.46 mM.

the two achiral Ni-salen units of  $5a' \cdot 5c'$  adopt one of the enantiomerically-twisted dynamic conformations<sup>20</sup> resulting from the right-handed double-helical framework generated by the chirality of the amidine residues of 5a', which further induces a left-handed helical arrangement of the two salen units (Figures 2e and S6d); the chiral conformations of the two salen units of  $5a' \cdot 5c'$  and their helical arrangement are similar to those of  $2a \cdot 2c$  (Figure 2d). Therefore, the analogous achiral Co/Co-bimetallic salen catalyst  $5a \cdot 5c$  enantioselectively produced the (S)-rich 8 as did  $3a \cdot 3c$ .

The chiral and achiral Co/Co-bimetallic salen-linked double-helical catalysts ( $3a \cdot 5c$  and  $5a \cdot 3c$ ) also gave 8 in good yields (70 and 87%) with slightly lower enantioselectivities (66 and 74% ee, respectively) (entries 7 and 8) than  $3a \cdot 3c$ . Based on these results, we concluded that the bimetallic Co/Co-salen catalysts mainly contribute to the catalytic efficiency to produce the desired product mostly independent of the chirality, while the enantioselectivity is determined by both the one-handed double-helical framework induced by the chiral amidine residues and the chirality of the salen-linkers. Thus, the fully double-helical bimetallic chiral Co/Co-salen catalyst ( $3a \cdot 3c$ ) showed a high efficiency and enantioselectivity ity in the present Henry reaction.

We believe that the present bimetallic salen-based chiral catalysts possessing a double-helical framework with a controlled handedness assisted by the complementary chiral salt bridges could be further applied to developing unique double-helical catalysts, to which the desired metal species can be introduced using the metal-free amidine and carboxylic acid dimers (1a/1c and 4a/4c) by metalation. Work along this line is now in progress in our laboratory.

## ASSOCIATED CONTENT

### **Supporting Information**

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

Experimental procedures, characterizations of dimer strands, and additional spectroscopic data (PDF)

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## Notes

The authors declare no competing financial interest.

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(12) See the Supporting Information.

(13) The chiral Co(II)-salen-linked  $3a \cdot 3c$  showed a relatively weak CD in the longer wavelength region when compared to that of the Ni(II)-salen-linked  $2a \cdot 2c$  (Figure 2). The model Co(II)-salen complex  $6_{Co}$  also exhibited a weaker CD than that of  $6_{Ni}$  (Figure S16). Therefore, the difference in the CD intensities observed for  $2a \cdot 2c$  and  $3a \cdot 3c$  may be originated from the metal species coordinating to the salen unit.

14) Chiral metal-salen complexes developed by Jacobsen et al. efficiently catalyze the enantioselective epoxide hydrolysis, in which two metal centers are involved in the transition state. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421-431.

(15) The  $3a \cdot 3c$  complex exhibited as an intense CD in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>NO<sub>2</sub> (3/2, v/v) in the presence of 1 equiv. of diisopropylethylamine (DIPEA) as that in CHCl<sub>3</sub> at 25 °C even at a very low concentration (0.50 mM) (Figure S12), indicating that the double-helical structure was retained during the Henry reaction. In addition, the amidinium–carboxylate salt bridges are stable in the presence of a Co(II)-salen complex (Figure S13).

(16) Conversion of 7 was quite high (entry 2), despite the low yield of **8**. This is probably due to side reactions during the Henry reaction. See: Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915-945.

(17) We first anticipated that the observed enhancement of the enantioselectivity for 3c could be ascribed to its self-associated homo-double helix formation with an excess handedness as observed for an analogous carboxylic acid dimer (CC) (Figure S15b).<sup>18</sup> However, the enantioselectivity of  $\mathbf{6}_{C0}$  increased from 56 to 77% ee (10% yield) in the presence of the carboxylic acid monomer (C) being comparable to that catalyzed by 3c (74% ee), suggesting the complex formation of the Co(II)-salen unit with the carboxy groups of  $3c^{19}$  which may contribute to enhancing the enantioselectivity during the Henry reaction, although such a homo-double helixlike aggregate formation of 3c could not be completely excluded because the CD spectral pattern and intensity of 3c were significantly different from those of  $6_{C_0}$  and its complex with C (Figure S17). Diffusion-ordered <sup>1</sup>H NMR spectroscopy (DOSY) measurements for 2c support such an aggregate formation (Figure S15a). The enantioselectivity of 3c decreased (55% ee) when the reaction was carried out in THF (entry 3), which will hamper the complex formation between the Co(II)-salen unit and the carboxy groups as well as the self-associated duplex formation of 3c, leading to dissociation into single strands, therefore, its CD signal significantly decreased in THF (Figure S14).

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