DOI: 10.1002/anie.200701735

Helical Structures

Enantioselective Synthesis of Complementary Double-Helical Molecules that Catalyze Asymmetric Reactions**

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In memory of Yoshihiko Ito

The double helix of DNA is one of the most attractive targets in organic and supramolecular chemistry because of its key biological structures and functions. It is composed of complementary strands derived from the homochiral component (D-sugars) and as a consequence, results in the overall right-handed double-helical structure. The metal-directed double-stranded helicates[1] and hydrogen-bonding-driven assemblies of some aromatic oligoamides[2] are known to form double helices. In contrast with DNA, these double helices lack the complementarity between the two strands and have not yet been used for supramolecular catalysis.[3] However, recent discoveries of DNA-based biocatalysts, DNAzymes,[4] and metal-bound DNA hybrid catalysts[5] for enantioselective reactions imply the potential ability of double helices as a promising chiral framework for enantioselective catalysis. Herein we show that complementary double-helical molecules showing optical activity owing to its helicity can be enantioselectively synthesized and can catalyze an asymmetric reaction in the presence of a metal ion; the double-helix framework with controlled helicity is essential for its high enantioselectivity. This approach suggests the broad potential of double-helix catalysis in asymmetric synthesis, which will provide an important step toward more-effective DNAzyme-like supramolecular catalysts with sequential information.

The design and synthesis of enantiomeric double helices is based on our recently developed strategy with amidinium carboxylate salt bridges, which assist the intertwining of the two crescent-shaped complementary molecular strands,[6] as illustrated in Scheme 1. The two complementary molecular strands **1** and **2** bear achiral amidine and carboxy groups, respectively, and the *m*-terphenyl units are linked through $\mathrm{Pt^{II}}$ acetylide complexes with chiral (*R*)- or (*S*)-2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl (MOP) or achiral triphenylphosphine ($\mathrm{PPh_3}$) ligands. Upon complexation, **1** and **2** are intertwined with each other through amidinium carboxylate salt bridges, resulting in the double helix **1**·**2** on which the bias in the twist sense could be induced and controlled by the chiral phosphine groups (MOP) on the $\mathrm{Pt^{II}}$ atoms. The interstrand ligand-exchange reaction on the $\mathrm{Pt^{II}}$ atoms by using an achiral diphosphine ligand, such as bis(diphenylphosphino)methane (dppm), leads to the bridged double helix **3**, which no longer has any chiral components except for helicity. We anticipated that the bias in the twist sense of **3** would be retained if the bridging diphosphine bind the two complementary molecular strands strongly enough to retard the racemization.

To this end, the diamidine strand (*R*)-**1a** was complexed with the achiral dicarboxylic acid strand **2** through the salt-bridge formation in $\mathrm{CDCl_3}$. The duplex formation was confirmed by cold-spray ionization mass spectrometry (CSI-MS) measurements; the CSI-MS spectrum of a $\mathrm{CDCl_3}$ solution of (*R*)-**1a**·**2** showed signals at *m*/*z* 3591.35 and 1796.43 corresponding to $[(R)\text{-}\mathbf{1a}\cdot\mathbf{2}+\mathrm{H}]^+$ and $[(R)\text{-}\mathbf{1a}\cdot\mathbf{2}+2\,\mathrm{H}]^{2+}$, respectively (see Figure S1 in the Supporting Information).[7] The ^{31}P NMR spectrum (200 MHz, $\mathrm{CDCl_3}$) of (*R*)-**1a**·**2** exhibited two signals at $\delta = 19.25$ and 18.52 ppm, which are attributable to the (*R*)-MOP and $\mathrm{PPh_3}$ ligands, respectively, clearly indicating that no scrambling of the phosphine ligands occurred during the duplex formation.[7] The CD spectra of the duplexes (*R*)- and (*S*)-**1a**·**2** in $\mathrm{CDCl_3}$ showed intense mirror-image CD signals, whereas (*R*)-**1a** exhibited weak Cotton effects in the same region (Figure 1 A and Figure S5 in the Supporting Information[7]). The significant enhancement of the Cotton effect for complexes (*R*)- and (*S*)-**1a**·**2**, especially in the $\mathrm{Pt^{II}}$ acetylide complex region (approximately 330–400 nm), indicates that the duplexes likely adopt an excess one-handed double-helical structure induced by the chiral MOP ligands coordinated to the $\mathrm{Pt^{II}}$ atoms.

In contrast with the analogous, fully organic, C−C-linked double helices,[6a] an equilibrium exists between the diastereomeric right- and left-handed double helices of the Pt-linked (*R*)- and (*S*)-**1a**·**2** in solution (Scheme 1). Therefore, the CD intensity of the first Cotton effect at around 370 nm ($\Delta\varepsilon_{\mathrm{1st}}$ ($\mathrm{M^{-1}\,cm^{-1}}$)), which corresponds to the helix-sense excess of **1a**·**2**, gradually increased with the decreasing temperature and reached an almost constant value ($\Delta\varepsilon_{\mathrm{1st}} = +70$) in $\mathrm{CDCl_3}$

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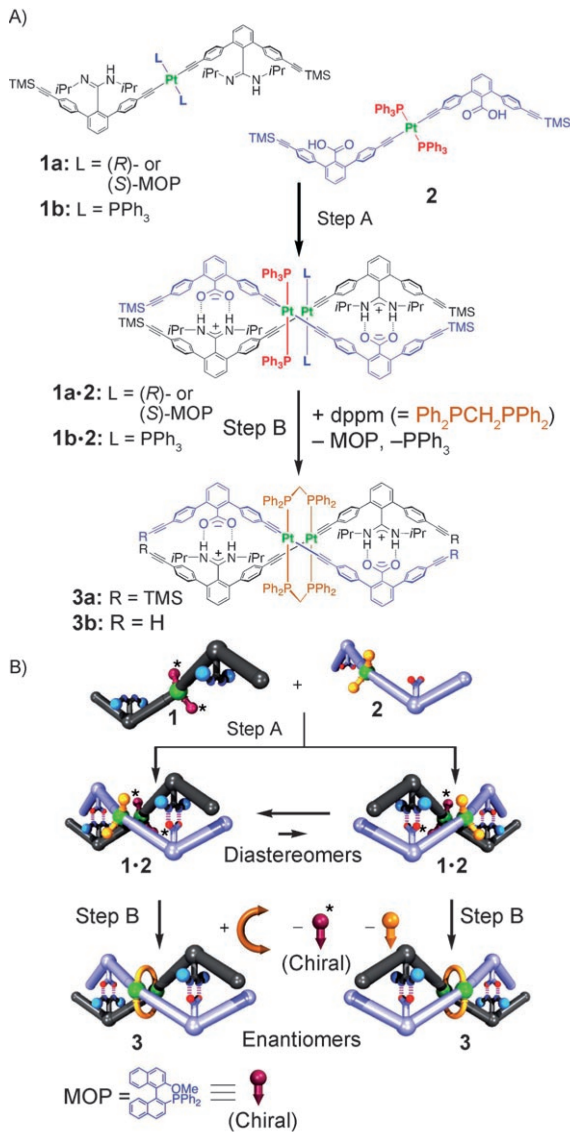
[**] We thank Bruker AXS K.K. for providing generous access to the Bruker Smart Apex II CCD-based X-ray diffractometer. We also acknowledge Dr. Hiroshi Ito (JST) for his help with the X-ray single-crystal analysis.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Enantioselective synthesis of complementary double-helical molecules. Schematic representation (A) and illustration (B) of the diastereomeric double-helix formation from complementary molecular strands (**1** and **2**) containing Pt^{II} acetylide complex moieties through amidinium carboxylate salt-bridge formation (step A); the chiral phosphine ligand (MOP) induces diastereomeric double helices. Removal of the chiral ligands by ligand exchange on the Pt^{II} with achiral diphosphine ligands (dppm) generates the enantiomeric double helices **3** with controlled helicity (step B); the right- and left-handed double helices can be controlled by the type of solvent used.

at −60 °C at which the duplex is supposed to take an almost one-handed double-helix form (Figure 1 A and Figure S6 in the Supporting Information[7]).[8] Interestingly, the Cotton-effect pattern of (*R*)-**1a·2** is highly dependent on the solvent used and is almost inverted in toluene at low temperatures (Figure 1 B and Figure S6 in the Supporting Information[7]), suggesting that the helical sense of (*R*)-**1a·2** was reversed in toluene. A similar solvent-dependent inversion of the helicity has been observed in single-helical polymers and oligomers,[2b,9] but is quite rare in double helices except for DNA.[10]

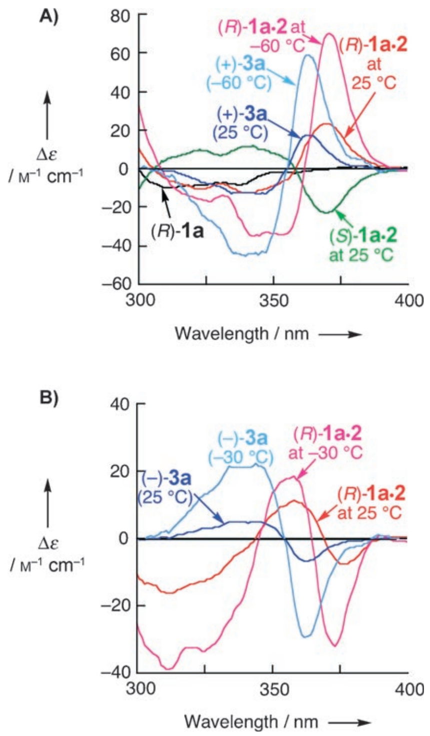


Figure 1. Formation of the Pt^{II}-linked double helices with an excess one-handedness, temperature dependence on the bias in the twist sense, and fixation of the double helix through a ligand-exchange reaction. A) CD spectra of (*R*)-**1a** (——), (*R*)-**1a·2** (——), (*S*)-**1a·2** (——), (+)-**3a** (prepared from (*R*)-**1a·2** in CHCl$_3$ at 25 °C, ——), and (+)-**3a** (prepared from (*R*)-**1a·2** in CHCl$_3$ at −60 °C (——) in CDCl$_3$ (0.1 mM) at 25 °C, and (*R*)-**1a·2** (——) in CDCl$_3$ (0.1 mM) at −60 °C. B) CD spectra of (*R*)-**1a·2** (——) in toluene (0.1 mM), (−)-**3a** (prepared from (*R*)-**1a·2** in toluene at 25 °C, (——) and (−)-**3a** (prepared from (*R*)-**1a·2** in toluene at −30 °C, (——) in CDCl$_3$ (0.1 mM) at 25 °C, and (*R*)-**1a·2** (——) in toluene (0.1 mM) at −30 °C. For the absorption spectra, see Figure S5 in the Supporting Information.[7]

We next investigated if the optical activity derived from the helicity of (*R*)- and (*S*)-**1a·2** could be retained when the chiral MOP ligands were replaced by the achiral bidentate ligand dppm. Removal of the chiral MOP attached to the (*R*)- and (*S*)-**1a·2** duplexes was carried out by ligand exchange by using dppm in CHCl$_3$ and toluene at various temperatures (Scheme 1, step B). For instance, the treatment of (*R*)-**1a·2** with dppm in CHCl$_3$ at 25 °C rapidly brought about the ligand-exchange reaction on the Pt^{II} acetylide complex moieties, providing the bridged double helix (+)-**3a** ("(+)" denotes the sign of the Cotton effect at around 370 nm) in 70 % yield after isolation by size-exclusion chromatography (SEC) fractionation. We note that (*R*)-MOP was quantitatively recovered (Figure S2 in the Supporting Information).[7] The structure of **3a** was confirmed by ^{1}H and ^{31}P NMR and infrared (IR) spectroscopy, CSI-MS and MALDI-TOF-MS (Figure S3 in the Supporting Information), and satisfactory elemental analysis.[7]

The X-ray single-crystal analysis revealed the structure of (±)-**3b**, the desilylated product of the racemic (±)-**3a** obtained from (±)-**1b·2** by using dppm under identical conditions for the synthesis of the optically active counterparts (Figure 2 A and B and Figure S7 in the Supporting

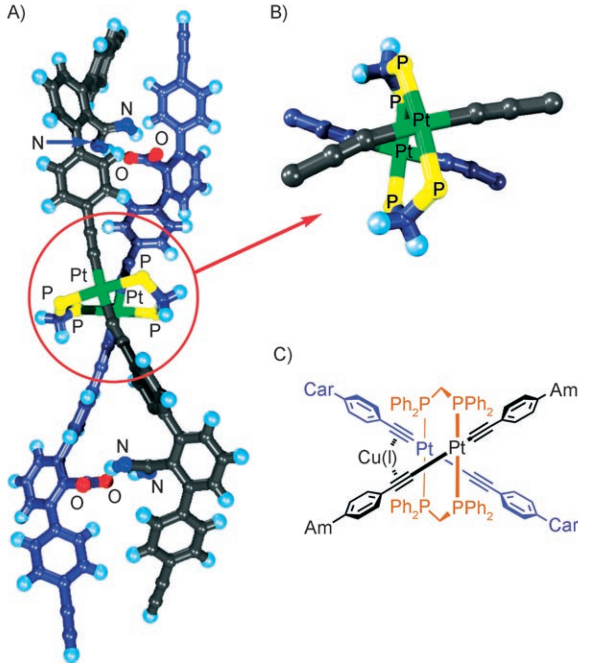


Figure 2. Structure of the bridged double helix. A) Capped-stick drawing of the crystal structure of the "fixed" double helix ((±)-**3b**)). Carbon, gray or blue; oxygen, red; nitrogen, blue; phosphorus, yellow; platinum, green; hydrogen, light blue. Solvent molecules and the phenyl groups of the dppm ligands are omitted for clarity. B) The partial structure of (±)-**3b** around the Pt^{II} atom. C) Illustration of the proposed structure of the Cu^{I} complex generated from **3** and Cu^{I}. "Am" and "Car" denote the *m*-terphenyl-bound amidine and carboxylic acid moieties, respectively.

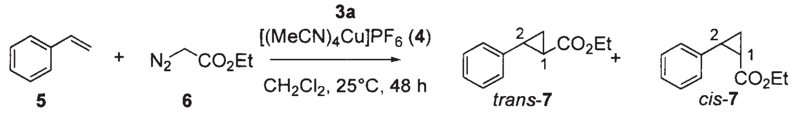
Information[7]). Compound (±)-**3b** adopts a double-helical structure in which each Pt^{II} atom is coordinated to two *trans*-alkynyl ligands (C-Pt-C, 169.46° and 172.49°) and two *trans*-bridging dppm molecules (P-Pt-P, 175.05° and 176.34°) to form an eight-membered ring. The platinum atoms show a distorted square-planar coordination (P-Pt-C, 83.93–94.58° and 82.05–96.10°) and are slightly twisted with respect to each other. These structural characteristics are similar to those reported for a dinuclear Pt^{II} alkynyl complex [Pt$_2$(dppm)$_2$(C≡CPh)$_4$].[11] The amidine and carboxy groups formed two identical salt bridges with two hydrogen bonds for each with an average N–O distances of 2.74 Å. Bridged by the dppm ligands and the two salt bridges, the molecular strands are intertwined with each other to form the double-helical structure.

The CD spectrum of (+)-**3a** obtained in CHCl$_3$ at 25 °C revealed the chiral transformation during the ligand-exchange reaction (Figure 1 A). Although (+)-**3a** no longer has any chiral ligands on the Pt complex moieties, distinct and slightly shifted CD bands were observed, suggesting that the bias in the helix sense induced by MOP was maintained during the course of the ligand-exchange reaction; the helix sense of (+)-**3a** has not been determined, but its helix-sense excess could be tentatively estimated to be 25% based on the $\Delta\varepsilon_{1st}$ value of (+)-**3a** at around 370 nm by using the maximum CD intensity of (*R*)-**1a·2** in CDCl$_3$ at −60 °C ($\Delta\varepsilon_{1st} = +70$) as the base value[8,12] (Figure S6 in the Supporting Information[7]). The CD and absorption spectra of (+)-**3** showed almost no temperature dependence within the temperature range of 0 to 50 °C and the CD intensity of (+)-**3** did not change at all after 100 days at 25 °C and 13 days at 50 °C in the dark, indicating that no racemization took place under the stated conditions. As expected, (−)-**3a** prepared from (*R*)-**1a·2** in toluene at 25 °C showed a complete mirror-image CD pattern except for the intensities owing to the enantiomeric double-helical structures (Figure 1 B). As a consequence, both enantiomeric double helices can be produced from a dynamic double-helical molecule induced by a single enantiomeric ligand (MOP). We are not aware of any synthetic double helices showing optical activity owing to helicity except for an example of enantioselective synthesis of Cu helicates with chiral auxiliaries and a few examples of optical resolution.[13]

The double helices (+)- and (−)-**3a** bridged at low temperatures (−10 to −60 °C) exhibited Cotton effects whose intensities were greater than those bridged at 25 °C. The higher CD intensities indicate the higher helix-sense excess of the duplex **3a** that was produced during the ligand-exchange reaction at low temperatures (Figure 1); the helix-sense excesses of **3a** obtained in CDCl$_3$ at 25, −10, and −60 °C and in toluene at −10 and −30 °C were estimated to be 25, 41, 81, 15, and 42, respectively.[8,12]

The alkynyl units on **3a** are expected to accommodate metal ions such as Cu^{I} in a tweezerlike fashion[11] (Figure 2 C). This prompted us to investigate if the double-helical **3a**–Cu complex is active for copper-catalyzed asymmetric reactions such as the cyclopropanation of styrene with ethyl diazoacetate (Table 1).[14] The active copper catalyst was generated by

Table 1: Asymmetric cyclopropanation of styrene with ethyl diazoacetate catalyzed by the **3a**-Cu^{I} complex.[a]



5 **6** *trans*-**7** *cis*-**7**

Run	**3a** Helix-sense excess (%)[b]	mol %	Yield[c] [%]	*trans/cis*[c] ratio	**7** *ee* [%][d] *trans*	*cis*	Configuration[e] *trans*	*cis*
1	(+)-**3a** (25)	10	41	62:38	23	3	1*S*,2*S*	1*R*,2*S*
2	(+)-**3a** (41)	10	38	63:37	44	8	1*S*,2*S*	1*R*,2*S*
3	(+)-**3a** (81)	10	39	63:37	80	8	1*S*,2*S*	1*R*,2*S*
4[f]	(+)-**3a** (81)	50	95	62:38	85	5	1*S*,2*S*	1*R*,2*S*
5	(−)-**3a** (15)	10	39	64:36	9	2	1*R*,2*R*	1*S*,2*R*
6	(−)-**3a** (42)	10	40	62:38	41	6	1*R*,2*R*	1*S*,2*R*

[a] Reactions were carried out in CH$_2$Cl$_2$ at 25 °C for 48 h under an argon atmosphere. [**5**]/[**6**] = 2:1. [**4**]/[**3a**] = 1:1. [b] Estimated based on the first Cotton-effect intensities at around 370 nm ($\Delta\varepsilon_{1st}$) after the SEC fractionation. The maximum CD intensity of (*R*)-**1a·2** in CDCl$_3$ at −60 °C ($\Delta\varepsilon_{1st} = +70$) was used as the base value. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* value was determined by analytical HPLC on a chiral column.[7] [e] Determined by optical rotation.[7] [f] Reaction was carried out at 25 °C for 24 h.

the complexation of the (+)- or (−)-**3a** of different helix-sense excesses with an equimolar amount of $[(\mathrm{MeCN})_4\mathrm{Cu^I}]\mathrm{PF_6}$. The asymmetric cyclopropanation was first carried out by using a catalytic amount of the (+)-**3a**-$\mathrm{Cu^I}$ complex with 25 % helix-sense excess (10 mol %) in $\mathrm{CH_2Cl_2}$ at 25 °C for 48 h, which produced the desired cyclopropane **7** in 41 % yield with modest diastereo- and enantioselectivities (Table 1, run 1). The enantioselectivity for *trans*-**7** further increased with the increasing helix-sense excess of **3a** and reached 80 % *ee* when the 81 % helix-sense excess (+)-**3a** was used (Table 1, runs 2 and 3). When 50 mol % of the (+)-**3a**-$\mathrm{Cu^I}$ catalyst (81 % helix-sense excess) was used, the cyclopropane **7** was obtained in 95 % yield, and 85 % *ee* of the *trans*-**7** was the major product (Table 1, run 4). The $\mathrm{Cu^I}$ catalyst with the opposite helicity prepared from (−)-**3a** afforded the *trans*-**7** with the reversed enantioselectivity (Table 1, runs 5 and 6). We observed an almost linear relationship between the helix-sense excesses of **3a** and the *ee* values of *trans*-**7**. In sharp contrast, the double helix (*R*)-**1a·2** complexed with $\mathrm{Cu^I}$ showed no activity.

These results suggest that the chiral space generated by the rigid double-helical structure of **3a** is effective and indispensable for the high enantioselectivity, thus providing a promising and conceptually new strategy in the broad fields of supramolecular catalysis.[3]

Received: April 19, 2007
Published online: June 25, 2007

Keywords: amidines · asymmetric synthesis · helical structures · platinum · salt bridges

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[7] See the Supporting Information for details of the synthesis, structures, characterization of compounds (*R*)- and (*S*)-**1**, **2**, **1·2**, and (+)- and (−)-**3**, and the procedure for the asymmetric cyclopropanation.

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[12] We attempted to separate enantiomers of (+)- and (−)-**3a** by using chiral HPLC to determine their helix-sense excess (enantiomeric excess), but it was found to be difficult.

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