

Diastereoselective Imine-Bond Formation through Complementary Double-Helix Formation

Hidekazu Yamada, Yoshio Furusho, and Eiji Yashima*

Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya 464-8603, Japan

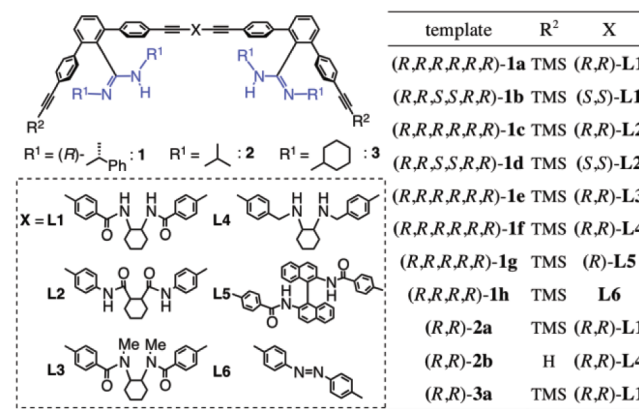
Supporting Information

ABSTRACT: Optically active amidine dimer strands having a variety of chiral and achiral linkers with different stereostructures are synthesized and used as templates for diastereoselective imine-bond formations between two achiral carboxylic acid monomers bearing a terminal aldehyde group and racemic 1,2-cyclohexanediamine, resulting in a preferred-handed double helix stabilized by complementary salt bridges. The diastereoselectivity of the racemic amine is significantly affected by the chirality of the amidine residues along with the rigidity and/or chirality of the linkers in the templates. NMR and kinetic studies reveal that the present imine-bond formation involves a two-step reversible reaction. The second step involves formation of a preferred-handed complementary double helix assisted by the chiral amidine templates and determines the overall reaction rate and diastereoselectivity of the amine.

Template-directed polymerization, or template synthesis,^{1,2} is ubiquitous in nature, as exemplified by the nucleic acid-templated polymerization that is capable of replication, transcription, and translation of the genetic information of the nucleic acids through non-covalent bonding interactions, providing DNA, RNA, and proteins with perfectly controlled sequences and chain lengths as well as chirality. Non-enzymatic template-directed syntheses have been used to construct oligonucleotide analogues,^{3–6} peptides,⁷ and small abiotic organic molecules⁸ and polymers.^{1a,2a,c,f,9} The key factor necessary for template-directed polymerization and synthesis is a complementary interaction between the template and the monomers; nucleotides and nucleobases and their related molecules or polymers have frequently been employed as templates. The helically twisted structure of the DNA templates also promoted a stereoselective chemical reaction when the reactive groups were positioned at each strand in such a way that nucleophilic substitution took place,⁵ but template-directed asymmetric or diastereoselective reactions are quite limited except for DNA.¹⁰

We previously designed and synthesized artificial double-stranded (ds) helices¹¹ consisting of complementary molecular strands intertwined through amidinium-carboxylate salt bridges.¹² The well-defined geometry and high association constants of the salt bridges prompted us to prepare novel complementary double helices bearing various types of linkers and possessing a helix-sense bias induced by the chiral amidine

Chart 1. Structures of Chiral Amidine Templates



groups. We also reported template synthesis of a complementary carboxylic acid dimer through an imine-bond formation along the template amidine dimer assisted by salt bridges, showing remarkable acceleration of the imine-bond formation assisted by the template during double-helix formation.¹³

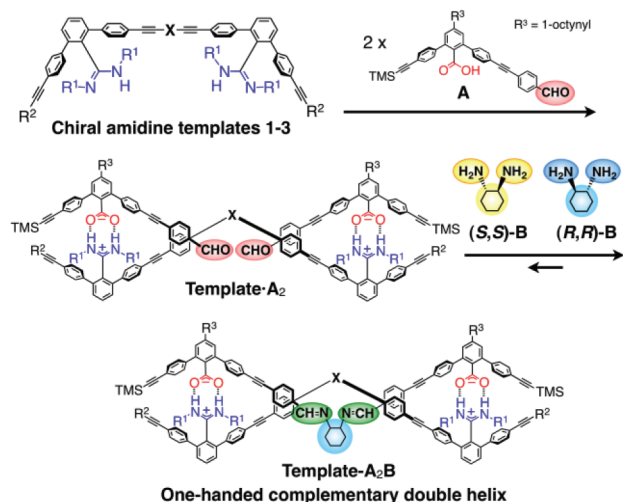
We have now designed and synthesized optically active amidine dimers consisting of (*R*)-1-phenylethyl amidine (**1**) and achiral isopropyl (**2**) and cyclohexyl amidines (**3**) with an *m*-terphenyl backbone linked through chiral (**L1–L5**) and achiral (**L6**) linkers (Chart 1). Amidine dimers **1–3** were used as optically active templates on which imine-bond formation takes place when a terminal aldehyde group on the complementary achiral carboxylic acid monomer **A** reacts with the racemic *trans*-1,2-cyclohexanediamine **B** along the templates, producing carboxylic acid dimer **A₂B** complexed with the template through salt bridges (Scheme 1). We anticipated that the imine-bond formation between **A** and **B** could proceed diastereoselectively assisted by the chiral templates, forming ds helical dimers with controlled helical sense.

Imine-bond formation was used in this study because it requires no catalyst and is well established in modern organic chemistry¹⁴ and DNA-templated polymerization of nucleobase analogues.^{4,6} Imine-bond formation between **A** and (*S,S*)-**B** was first conducted using the chiral amidine dimer **1a** as a template linked by (*R,R*)-*trans*-cyclohexanediamine through an amide

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Scheme 1. Diastereoselective Imine-Bond-Formation through Complementary Double-Helix Formation



bond (L1) in CDCl_3 at 25°C ; the reaction's progress was monitored by ^1H NMR spectroscopy (Figures 1a and S1a). ^1H NMR spectra of the mixtures of 1.0 mM A and 0.5 mM (S,S)-B in the presence of 0.5 mM 1a showed resonances of NH protons at the low magnetic field of 13.25 ppm, indicating salt bridge formation (Figure S1a). The peak intensity of the aldehyde proton (H_a) of A decreased with time, while two new kinds of imino proton peaks appeared (H_b , H_c), suggesting imine-bond formation. The peak intensity of H_c gradually increased with time, whereas that of H_b decreased and almost disappeared. Taking into account these spectral changes along with the fact that the imine-bond formations between A and B are likely two-step reversible reactions (Figure 1), peaks H_b and H_c were reasonably assigned to the protons corresponding to monoimine intermediate AB and carboxylic acid dimer A₂B, respectively, indicating duplex 1a·A₂B formation, which was also supported by negative-mode electrospray ionization mass spectrometry, which exhibited a molecular ionic peak at $m/z = 2808.0$ corresponding to $[\text{1a} \cdot \text{A}_2\text{B} - \text{H}]^-$ (Figure S2). The reaction reached equilibrium within 9 h, and no detectable ^1H NMR change was observed after 1 day. Reaction between A and (R,R)-B in the presence of the identical 1a template (Figures 1b and S1b) proceeded faster than that with (S,S)-B, reaching equilibrium within 3 h. In addition, the peak intensity of the imino proton (H_b) derived from the monoimine intermediate AB was very weak even during the initial stage, indicating that the second imine-bond formation proceeded immediately after the first.¹⁵

Time-dependent circular dichroism (CD) and absorption spectra were then measured to follow duplex formation at 25°C (Figure 1c,d). Upon addition of (S,S)-B to a solution of template 1a and 2 equiv of A that formed a 1:2 complex stabilized by amidinium-carboxylate salt bridges in CDCl_3 , the absorption spectra changed slowly and reached equilibrium within 9 h, accompanied by a decrease in the first Cotton effect intensity in the long-wavelength region over 310 nm. Upon addition of (R,R)-B, the absorption spectra changed more rapidly, accompanied by a significant enhancement of Cotton effect intensities at 260–350 nm, reaching equilibrium within 3 h. These results suggest that duplex formation with (R,R)-B is much faster than with (S,S)-B. In addition, in both cases, the Cotton effect intensities after reaching equilibria were higher

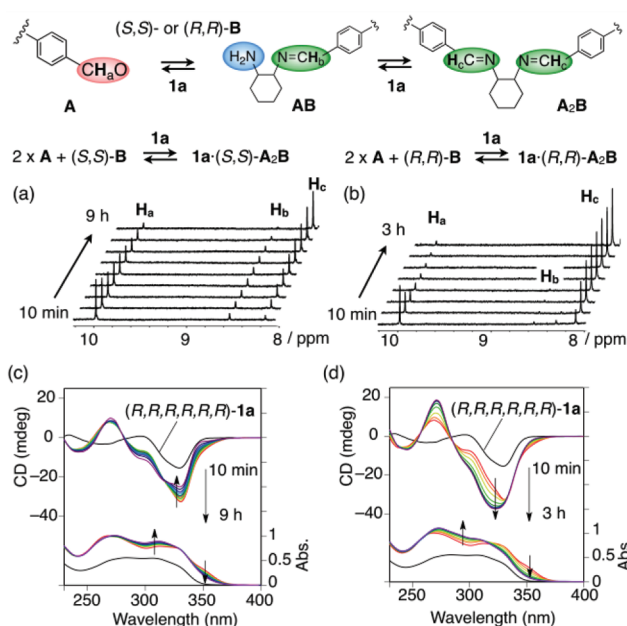


Figure 1. Time-dependent partial ^1H NMR (a,b) and CD and absorption (c,d) spectral changes of mixtures of 1.0 mM A and 0.5 mM (S,S)-B (a,c) or (R,R)-B (b,d) in the presence of 0.50 mM 1a in CDCl_3 at 25°C .

than that of amidine template 1a in the absorption region of the *p*-phenyleneethynylene residues (~ 270 – 370 nm), indicating that the duplexes of 1a with (S,S)-A₂B and (R,R)-A₂B most likely adopted double-helical structure with a helix sense bias induced by chiral template 1a, although their helical sense excesses might be different judging from their CD intensities because of the difference in the linker structures B with opposite configuration, resulting in the formation of a more preferred-handed double helix for the 1a·(R,R)-A₂B.

Imine-bond formation between A and racemic B was then investigated in the presence of 1a in CDCl_3 at 25°C , because one of the enantiomers B was anticipated to react with A faster than the other, as predicted by the results in Figure 1, to form a preferred-handed complementary duplex with 1a. Upon mixing of equimolar amounts of A and racemic B (1.0 mM each) in the presence of 0.5 mM 1a, the aldehyde proton (H_a) intensity of A rapidly decreased, while two new imino proton peaks appeared ($\text{H}_c(\text{S,S})$ and $\text{H}_c(\text{R,R})$), assigned to dimers (S,S)-A₂B and (R,R)-A₂B, respectively (Figure S3a). The changes in the integral ratio of peaks $\text{H}_c(\text{S,S})$ and $\text{H}_c(\text{R,R})$ with time revealed that (R,R)-B reacted diastereoselectively with A over (S,S)-B to form duplex 1a·A₂B with diastereomeric excess (*de*) of 57% during the initial stage (15% conversion of B) under predominantly kinetic control assisted by chiral template 1a. As the reaction progressed, the *de* gradually decreased as anticipated, reaching a constant value (30%) after ~ 3 h under totally thermodynamic control (run 1 in Table 1 and Figure S3b). We note that the *de* will vary significantly as a function of the conversion of B: lower conversion will lead to higher *de*. We attempted to measure the NMR spectrum of the mixture at lower conversion of B, but it was difficult because of the long acquisition time (10 min). Therefore, we calculated the selectivity factor (*s*) for qualitative comparison of the diastereoselectivity of the amidine template (Table 1) assuming that the present imine-bond formation could be regarded as a kind of kinetic resolution, at least initially. The changes in the

Table 1. Results of Diastereoselective Imine-Bond-Formations between A and Racemic B in the Presence of Chiral Amidine Templates 1–3

run	template	initial			at equilibrium			
		conv. of B ^a (%)	de ^a (%)	s ^b	time conv. of B ^a (h)	conv. of B ^a (%)	$\Delta\epsilon_{180}/\Delta\epsilon^c$	de ^a (%)
1	(<i>R,R,R,R,R,R</i>)-1a	15	57 (<i>R,R</i>)	4.0	3	48	−205/323	30 (<i>R,R</i>)
2	(<i>R,R,S,S,R,R</i>)-1b	13	32 (<i>R,R</i>)	2.0	4	49	−136/307	15 (<i>S,S</i>)
3	(<i>R,R,R,R,R,R</i>)-1c	27	0	1.0	1	50	−165/323	0
4	(<i>R,R,S,S,R,R</i>)-1d	14	4 (<i>R,R</i>)	1.1	2	50	−87/323	30 (<i>S,S</i>)
5	(<i>R,R,R,R,R,R</i>)-1e	4	52 (<i>R,R</i>)	3.2	2	43	−170/323	22 (<i>R,R</i>)
6	(<i>R,R,R,R,R,R</i>)-1f	19	0	1.0	12	43	−118/320	0
7	(<i>R,R,R,R,R,R</i>)-1g	1	0	1.0	12	35	−208/341	0
8	(<i>R,R,R,R</i>)-1h	3	58 (<i>R,R</i>)	3.8	12	15	−51/318	30 (<i>R,R</i>)
9	(<i>R,R</i>)-2a	9	8 (<i>R,R</i>)	1.2	2	50	−67/332	8 (<i>R,R</i>)
10	(<i>R,R</i>)-2b	6	0	1.0	3	44	7/322	0
11	(<i>R,R</i>)-3a	12	9 (<i>R,R</i>)	1.2	2	50	−82/332	9 (<i>R,R</i>)

^aEstimated by ¹H NMR. ^bSelectivity factor determined using $s = k_{\text{rel(fast/slow)}} = \ln[1 - C(1 + de)] / \ln[1 - C(1 - de)]$, where C is the conversion of B and taking the de of A₂B. ^cUnits are cm^{−1}M^{−1}/nm.

patterns and intensities of the CD and absorption spectra of the mixture with time (Figure S3c) were similar to those observed for the mixture of A and (*R,R*)-B, which also supported preferential reaction of (*R,R*)-B over (*S,S*)-B, leading to a double helix of 1a·(*R,R*)-A₂B with an excess helical sense.

Imine-bond formations between A and racemic B in the presence of templates consisting of optically pure (*R,R*)-amidine 1 and achiral amidines 2 and 3 linked through chiral (L1–L5) and achiral (L6) linkers were then investigated (Figures S4–S13) to gain insight into the effects of the amidine and linker chiralities and the stereostructures of the linkers on the diastereoselective imine-bond formations (Chart 1). These results are summarized in Table 1.

Template 1b, in which the linker of 1a was replaced by the corresponding (*S,S*)-enantiomer, also assisted (*R,R*)-selective imine-bond formation of B (32% de) during the initial stage. However, as the reaction proceeded, the selectivity reversed, and the opposite (*S,S*)-B was preferentially inserted after aldehyde A to form optically active duplex 1b·A₂B (15% de) (run 2 and Figure S4), although the diastereoselectivity and hence the s value were lower than with 1a, and the CD intensities during the reaction were weaker than for 1a·A₂B duplexes. Thus the amidine chirality of the template appears to kinetically control the (*S,S/R,R*) selectivity of diamine B initially, but at equilibrium the selectivity is governed by the linker chirality under thermodynamic control, while the diastereoselectivity (de and s) may be determined by both the amidine and linker chiralities (see below).

Templates 1c,d, with structural characteristics similar to those of 1a,b except for the linker amide sequences, were used; amidine dimers 1c,d are linked respectively by the (*R,R*)- or (*S,S*)-*trans*-cyclohexanedicarboxylic acid through an amide bond (L2). Surprisingly, template 1c showed no diastereoselectivity toward racemic B during duplex formation of 1c·A₂B (run 3 and Figure S5), whereas template 1d displayed behavior similar to that of 1b: (*R,R*)-B selectively reacted with A initially, but (*S,S*)-B was preferentially inserted at equilibrium, affording the 1d·A₂B duplex (30% de of A₂B) (run 4 and Figure S6), suggesting that the slight difference in the linker amide sequences of the templates significantly affects diastereoselectivity during imine-bond formation. Again, the linker stereochemistry ((*S,S*)-L2) determined the (*S,S/R,R*) selectivity of B.¹⁶ The first Cotton intensities of these duplexes at

equilibrium were almost proportional to the de values of A₂B produced at equilibrium (Figure S15), suggesting that the helical sense excess of the resulting duplex likely determines the diastereoselectivity of racemic B at equilibrium.

The *N*-methylated amide-linked (L3) chiral amidine dimer of 1a, 1e, showed good (*R,R*)-selectivity (52% de, s = 3.2 initially; 22% de at equilibrium) and slightly weaker Cotton effects compared to 1a (run 5 and Figure S7). In contrast, template 1f, having a flexible *N*-methylene linker (L4), exhibited no diastereoselectivity (run 6 and Figure S8), indicating that the amide bond (−NH−CO−) is not essential but the rigidity of the template backbones may be required for diastereoselective imine-bond formation. We then synthesized 1g, a more rigid and bulkier template linked by the (*R*)-1,1'-binaphthyl-2,2'-diamine through an amide linkage (L5), which unexpectedly showed no diastereoselectivity (run 7 and Figure S9), probably due to the steric hindrance of the linker residue, and the duplex showed almost no change in its CD spectra before and after imine-bond formation.

Interestingly, 1h, in which the linker of 1a was replaced by an achiral rigid azobenzene unit (L6), also served as a good template, showing (*R,R*)-B selectivity of s = 3.8 during the initial stage despite its achiral linker (run 8 and Figure S10). This unexpectedly high diastereoselectivity suggests that chiral linkers may not be indispensable for the present diastereoselective imine-bond formation. We note, however, that template 1h assisted the imine-bond formation in a rather low conversion at equilibrium (15%), probably because its azobenzene unit is too short to form a stable duplex with the resulting complementary A₂B strand; therefore, the reaction mixture containing a small amount of duplex showed almost no change in its CD spectra despite the high (*R,R*)-B selectivity.

The effect of amidine chirality on the diastereoselective imine-bond formation was then investigated in the presence of templates bearing achiral isopropyl (2) and cyclohexyl (3) amidines linked by the optically active rigid L1 (2a, 3a) and flexible L4 (2b) linkers. As shown in Table 1 (runs 9–11 and Figures S11–S13), diastereoselectivities with 2a and 3a were poor (8 and 9% de, respectively), independent of the conversion, and 2b showed no diastereoselectivity, as anticipated because of its flexible linker. However, templates 2a and 3a produced the (*R,R*)-rich dimers of A, revealing that the linker chirality contributes to determining the (*S,S/R,R*) selectivity of diamine B, although the diastereoselectivity is not high when the amidines are achiral.

Using template 2b, the (*R,R*)-*trans*/(*R,S*)-*cis* selectivity of B was also examined. The product ratio of the (*R,R*)-A₂B/(*R,S*)-A₂B dimers was estimated to be 76/24 (mol/mol) from ¹H NMR (Figure S14), indicating that 2b can discriminate the diastereomers of *trans*- and *cis*-B, and *trans*-B was selectively inserted after monomer A during the template-assisted duplex formation.

From these results, we conclude that the chiral (*R*)-1-phenylethyl groups on the amidine residues mainly contribute to diastereoselective imine-bond formation during the initial stage under kinetic control, while the chirality of the *trans*-cyclohexane-based linkers determines the (*S,S/R,R*) selectivity and diastereoselectivity under thermodynamic control. Thus, the appropriate combination of rigid linkers with a specific handedness and chiral amidines appears to be important for achieving high diastereoselectivity during template-assisted imine-bond formation.

Table 2. Rate Constants ($\text{M}^{-1}\text{s}^{-1}$) of the Imine-Bond Formation between **A** and **B** in the Presence of **1a**

	$2\text{A} + \text{B} \xrightleftharpoons[k_{-1}]{k_1} \text{A} + \text{AB} + \text{H}_2\text{O} \xrightleftharpoons[k_{-2}]{k_2} \text{A}_2\text{B} + 2\text{H}_2\text{O}$			
diamine	$k_1 [\text{M}^{-1}\text{s}^{-1}]$	$k_{-1} [\text{M}^{-1}\text{s}^{-1}]$	$k_2 [\text{M}^{-1}\text{s}^{-1}]$	$k_{-2} [\text{M}^{-1}\text{s}^{-1}]$
(<i>R,R</i>)- B	1.4	0.23	8.1	9.0×10^{-4}
(<i>S,S</i>)- B	0.65	0.60	1.0	1.2×10^{-4}

Finally, to gain information about the rate constants of (*S,S*)- and (*R,R*)-**B** with **A** during two-step imine-bond formations along **1a**, the time-dependent ^1H NMR spectral changes (Figure 1a,b) were analyzed, and the concentrations of carboxylic acid monomer **A**, monoimine intermediate **AB**, and carboxylic acid dimer **A₂B** were plotted versus reaction time (Figure S1c,d), revealing that the imine-bond formations of (*R,R*)-**B** in each step assisted by **1a** reached equilibrium much faster than for (*S,S*)-**B**. It was difficult to estimate the rate constant at each step analytically due to the complicated two-step reversible reactions (Table 2). Thus, the kinetic data were fitted by numerical integration using the fourth-order Runge–Kutta method to estimate the rate constants (SI and Table 2). The rate constants for the first forward reaction (k_1) in the presence of **1a** at 25°C were estimated to be $1.4\text{ M}^{-1}\text{s}^{-1}$ for (*R,R*)-**B** and $0.65\text{ M}^{-1}\text{s}^{-1}$ for (*S,S*)-**B**, indicating that (*R,R*)-**B** reacted with **A** almost 2.2 times faster than (*S,S*)-**B** to form monoimine intermediate **AB**. During further reaction of **AB** with **A**, (*R,R*)-**AB** was found to react 8.1 times faster than (*S,S*)-**AB**, forming carboxylic acid dimer **A₂B** rich in (*R,R*)-**B**; the rate constants for the second forward reaction (k_2) along **1a** at 25°C were $8.1\text{ M}^{-1}\text{s}^{-1}$ for (*R,R*)-**B** and $1.0\text{ M}^{-1}\text{s}^{-1}$ for (*S,S*)-**B**.

This remarkable enhancement of the rate constants for **AB**, particularly (*R,R*)-**AB** in the second imine-bond formation, could be ascribed to ternary complexation of **1a**·**A**·(*R,R*)-**AB**, with the aldehyde group of **A** and the remaining amino group of (*R,R*)-**AB** much more favorably located than in **1a**·**A**·(*S,S*)-**AB** so as to form a complementary double helix with helix sense bias assisted by the chiral amidine of **1a**. Therefore, in the second imine-bond formation, the (*S,S*/*R,R*) selectivity and its diastereoselectivity of racemic **B** could be mainly controlled by the amidine chirality of the chiral amidine templates initially, but both the amidine and linker chiralities contribute at equilibrium.

We believe the present findings will contribute to developing more sophisticated template-assisted asymmetric replication using complementary chiral amidinium-carboxylate salt bridges.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

yashima@apchem.nagoya-u.ac.jp

Notes

The authors declare no competing financial interest.

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