Asymmetric Amplification

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Self-Replication and Amplification of Enantiomeric Excess of Chiral Multifunctionalized Large Molecules by Asymmetric Autocatalysis**

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Abstract: *Self-replication of large chiral molecular architectures is one of the great challenges and interests in synthetic, systems, and prebiotic chemistry. Described herein is a new chemical system in which large chiral multifunctionalized molecules possess asymmetric autocatalytic self-replicating and self-improving abilities, that is, improvement of their enantioenrichment in addition to the diastereomeric ratio. The large chiral multifunctionalized molecules catalyze the production of themselves with the same structure, including the chirality of newly formed asymmetric carbon atoms, in the reaction of the corresponding achiral aldehydes and reagent. The chirality of the large multifunctionalized molecules controlled the enantioselectivity of the reaction in a highly selective manner to construct multiple asymmetric stereogenic centers in a single reaction.*

The creation of huge synthetic molecules possessing remarkable self-replicating and self-improving functionalities remains a great challenge in organic, prebiotic, and systems chemistry.[1] To date, self-replications of oligonucleotides,[2] oligopeptides,[3] and complementary artificial molecules[4] in synthetic chemical systems have been demonstrated.[5] In these chemical systems, the molecules replicate by a non-enzymatic template-directed synthesis. Thus, these chemical approaches are considered to be nice models for prebiotic replicating reactions. In contrast, the chirality in the replicated products in previously reported chemical systems is based upon the pre-existing chirality of each building block. To the best of our knowledge, there has been no report of an efficient chemical process in which large chiral molecules are autocatalytically formed from completely achiral substrates and reactants. Herein, we report the elaboration of large chiral molecular architectures with autocatalytic self-replicating ability. In addition, we evaluate their function of self-improvement, that is, improvement of their enantiopurity. In our replication system, the large molecule is formed from a branched alkylsilane backbone and the periphery of the structure has a pyrimidine moiety with an asymmetric carbon atom. Such chiral molecules catalyze the production of molecules with the same structure, including the chirality of newly formed asymmetric carbon atoms, in the reaction of the corresponding achiral aldehydes and achiral dialkylzinc reagent. It is noteworthy that the ratio of the diastereomers, including enantiomers, and enantioenrichment continuously increased, finally forming a nearly enantiopure product. Thus, these molecules contain the functionalities of both self-replication and self-improvement of enantioenrichment.

We have previously reported the asymmetric autocatalysis[6,7] of 5-pyrimidyl alkanols with a significant amplification of the enantiomeric excess (*ee*),[8] which enables the amplification of chirality from extremely low values to near enantiopure values (> 99.5 % *ee*).[9–11] We have found here that chiral macromolecules possessing a hexameric multifunctionalized structure with as many as six asymmetric carbon centers automultiply in a manner of asymmetric autocatalysis. Even when large molecules with low isomeric and enantiomeric purities were used as the initial catalyst, five consecutive asymmetric autocatalysis events multiplied the number of molecules (homoisomer: by a factor of ca. 900 000 times) and amplified the diastereomeric ratio and *ee* value, based upon the homoisomer of the newly formed chiral molecules, to achieve greater than 99.5 % *ee*.

We designed the large chiral molecules based upon 5-pyrimidyl alkanols, which act as highly efficient asymmetric autocatalysts in the addition reaction of diisopropylzinc to the corresponding pyrimidine-5-carbaldehyde, as shown in Figure 1. The hexakis(2-ethynyl-5-pyrimidyl alkanol)hexaalkylsilane **1** was synthesized from an alkylsilane backbone with terminal acetylene and pyrimidyl alkanol as the monomeric moiety by a coupling reaction (see Scheme S1 in the Supporting Information). Its isopropylzinc alkoxide was assumed to be the actual catalytic species. When racemic alkanol was used as the coupling partner of the alkylsilane, the same number of (*S*)- and (*R*)-pyrimidyl alkanols were introduced to the terminals of the skeleton almost randomly, that is, seven isomers of **1** were formed in the stochastic racemic ratio with the binomial distribution.[12,13] Six equivalents of asymmetric carbon atoms produce seven diastereomeric and enantiomeric isomers because of the six absolute

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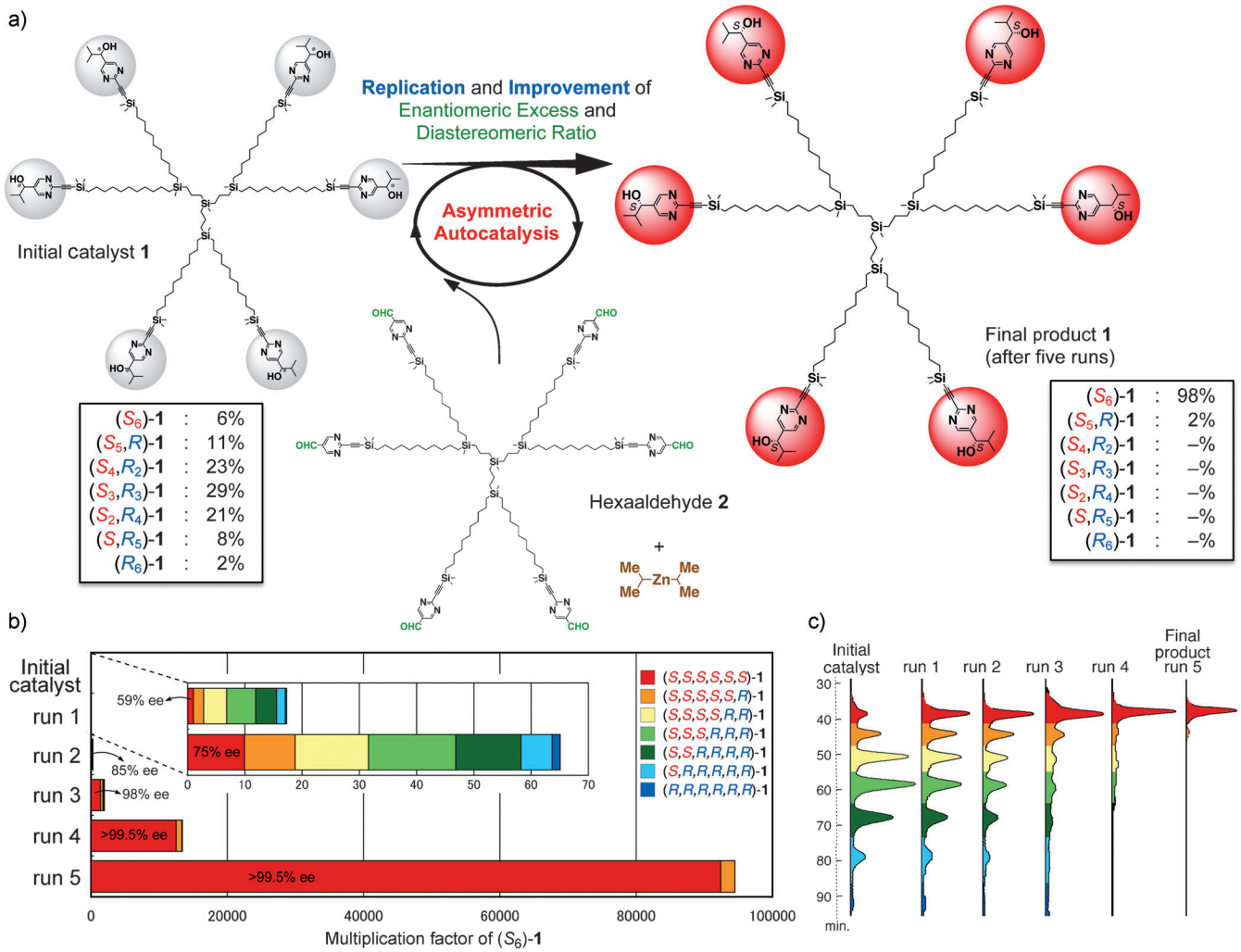
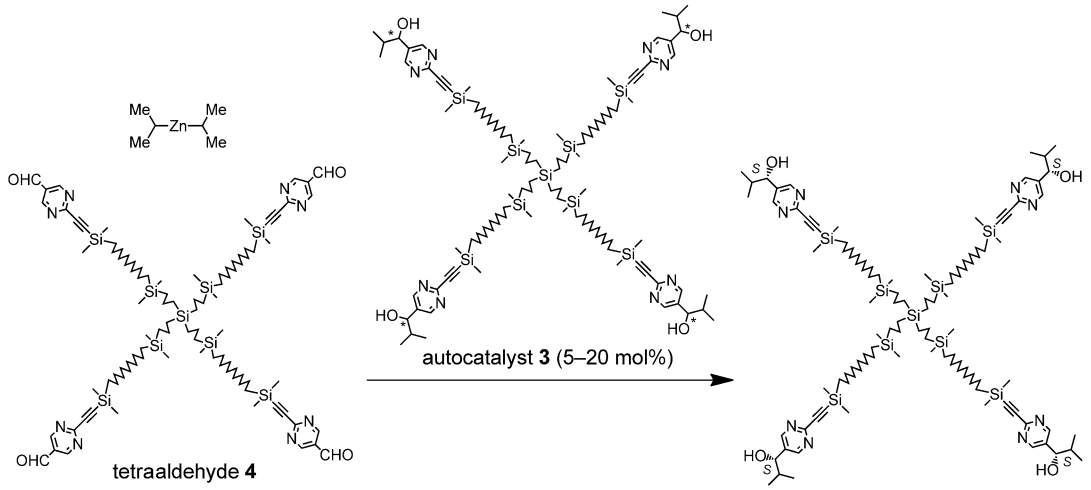


Figure 1. Replication and self-improvement of the *ee* value and diastereomeric ratio of chiral molecules (S_6)-**1**. a) The consecutive addition of diisopropylzinc to the hexaaldehyde **2** in the presence of the chiral macromolecule **1**. For the typical procedure of asymmetric autocatalysis, see the Supporting Information. b) The continuous multiplication of the chiral molecule (S_6)-**1** and improvement of the isomeric ratio and enantioenrichment of (S_6)-**1**. c) Analysis of the seven isomers of the compound **1** by HPLC using a chiral stationary phase.

configurations (*S* or *R*) of the terminal pyrimidine moieties. When a pyrimidyl alkanol having the *S* configuration with high *ee* value was subjected to the coupling reaction, (S_6)-**1** was obtained in almost enantiopure form. The corresponding achiral hexaaldehyde **2** could be prepared by a similar synthetic method using pyrimidine-5-carbaldehyde as the monomeric coupling partner.

The experimental results of the asymmetric autocatalysis using the hexamer **1** are shown in Figures 1 a–c and Table S1. Using these large synthetic molecules, we performed the asymmetric autocatalytic reaction and determined the diastereomeric ratio and *ee* value of the formed molecules **1**. Initially, the addition of diisopropylzinc to **2** was conducted in the presence of the initial catalyst **1** (ee_{homo} based on the homoisomers (S_6)-**1**/(R_6)-**1** was 59%; isomer ratios: (S_6)/(S_5,*R*)/(S_4,R_2)/(S_3,R_3)/(S_2,R_4)/(S,R_5)/(R_6)-**1** = 6:11:23:29:21:8:2). The isopropylation of each aldehyde moiety proceeded readily to afford the hexaalkylated product **1** as a mixture with the initial catalyst **1**. The ee_{homo} value was found to be enhanced to 75% *ee*, including the initial catalyst. Then, the product **1** (including initial catalyst) was submitted to the next autocatalytic reaction as the catalyst. After three additional cycles of reaction, we observed further improvement of the ee_{homo} value and isomer ratio. The ratio of (S_6)-**1** was significantly increased to 93% and the multiplication factor of the homoisomer **1** from the initial catalyst was achieved to greater than 12500 times, and the ee_{homo} value of **1** was significantly amplified to greater than 99.5% *ee*. One more cycle of the asymmetric autocatalytic reaction using 10 mol% of the catalyst **1** afforded the chiral molecule **1** as the final product with a yield of 60% as the newly formed product. The ratio of (S_6)-**1** was increased to 98%, the ee_{homo} value amplified to greater than 99.5% *ee*, and the isomer ratio improved to (S_6)/(S_5,*R*)/(S_4,R_2)/(S_3,R_3)/(S_2,R_4)/(S,R_5)/(R_6)-**1** = 98:2:–:–:–:–:–). Thus, (S_6)-**1** has exclusively increased by a factor of more than 92000 times during these steps, and the ratio of other isomers containing the *R* configuration almost disappeared, except for 2% of (S_5,*R*)-**1**. That is to say, self-replication of the large chiral molecule (S_6)-**1** has been obtained in this autocatalytic system and additionally,

Table 1: Asymmetric autocatalysis of (S_4)-tetrakis(5-pyrimidyl alkanol)tetraalkylsilane **3**.



Run[a]	ratio[b]	Catalyst **3** amount (mol%)[c]	ee_{mono} [%][d]	ee_{homo} [%][e]	Mixture of catalyst **3** and product **3** ratio[b,f]	ee_{mono} [%][d]	ee_{homo} [%][e]	yield [%]	Multiplication factor for (S_4)-**3**	Product **3** ratio[b]	yield [%][g]
1[h]	6:25:38:25:6	20	0.06	0.5	28:26:21:16:9	24	52	97	4.9	34:26:17:14:9	77
2	28:26:21:16:9	20	24	52	74:14:7:4:1	77	96	106	26	84:12:3:1:–	86
3	74:14:7:4:1	5	77	96	96:3:1:–:–	97	>99.5	94	483	97:2:1:–:–	89
4	96:3:1:–:–	5	97	>99.5	97:2:1:–:–	98	>99.5	91	8795	97:2:1:–:–	86
5	97:2:1:–:–	5	98	>99.5	98:1:1:–:–	99	>99.5	96	168870	98:1:1:–:–	91

[a] A typical procedure for asymmetric autocatalytic replication is described in the Supporting Information. For the synthesis of **3** and **4**, see Scheme S2. [b] The isomeric ratios of (S_4)/(S_3,R)/(S_2,R_2)/(S,R_3)/(R_4)-**3** are described. The ratio was determined by HPLC using a chiral stationary phase. [c] The value is given for the amount of the tetraaldehyde **4** used. [d] The *ee* value of the monomeric pyrimidine part, assuming that all peripheral pyrimidine functionalities in **3** were subtracted. [e] The *ee* value is based on the homoisomers (S_4)-**3** and (R_4)-**3**. [f] The values are described for a mixture of the initial catalyst **3** used in this reaction and the newly formed product **3**. [g] The yield was calculated by subtracting the amount of the autocatalyst **4** loading from the amount of isolated **4**. [h] Initial catalyst was prepared by mixing a small amount of (S_4)-**3** and a stochastically distributed racemic mixture of **3**.

the improvement of the isomeric ratio and amplification of enantioenrichment, that is, self-improvement, was observed during this chemical replication cycle.

The replication and improvement of the tetrakis(pyrimidyl alkanol)tetraalkylsilane **3** was examined and the results are summarized in Table 1. The initial catalyst **3**, with a small imbalance of enantiomers, was prepared by adding (S_4)-**3** to the compound **3** with a stochastic racemic mixture of isomers. The ee_{homo} value of (S_4)-**3** was calculated to be 0.5% from the amount of its enantiomer (R_4)-**3** and the ee_{mono} value (*ee* of the monomeric pyrimidine part) was calculated to be 0.06% assuming that all of the terminal pyrimidine functionalities were taken off. In run 1, the above indicated compound **3** with a small excess of enantiomer was utilized initially to perform the addition of diisopropylzinc to the tetrakis(pyrimidine-5-carbaldehyde)tetraalkylsilane **4**. After the tetraalkylation of **4**, **3** (ee_{homo} = 52%, isomeric ratio: (S_4)/(S_3,R)/(S_2,R_2)/(S,R_3)/(R_4)-**3** = 28:26:21:16:9) was isolated as a mixture, containing the initial catalyst **3**, in 97% yield. The ee_{homo} and ee_{mono} values of (S_4)-**3** amplified significantly, reaching 52 and 24%, respectively. The obtained mixture of initial catalyst and the product **3** was subjected to the next replication cycle as the starting catalyst for run 2. After an additional four runs of the replication cycles (runs 2–5), the final compound **3** was obtained with an ee_{homo} value of greater than 99.5% and an isomeric ratio of (S_4)/(S_3,R)/(S_2,R_2)/(S,R_3)/(R_4)-**3** = 98:1:1:–:–. The homoisomer (S_4)-**3** was automultiplied by about 170000 times to reach near enantiopure form. The amounts of (S,R_3)-**3** and (R_4)-**3** were below the detection level in HPLC analysis. In this chemical system, (S_4)-**3** replicated significantly with improvement of its diastereomeric and enantiomeric ratio during the continuing reaction cycles. The portion of the isomers **3** containing *R*-asymmetric carbon was greatly reduced in the mixture.

As described, these reactions are asymmetric autocatalysis of large chiral molecules with an amplification of the chirality. Thus, the asymmetric autocatalysis of 5-pyrimidyl alkanol with amplification of the *ee* value[8] can work on the large branched molecules with many reaction points. In addition, it is the first example of a real chemical reaction, that is, large chiral molecules catalyzing the production of chiral molecules, having the same structure and same configuration, from an achiral substrate and reagent. The enantioselectivity of this reaction was controlled by the chirality of the large multifunctionalized molecules. The synthetically important aspect of this reaction is that in a single reaction,

multiple asymmetric centers are constructed with high selectivity.

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[12] The seven isomers of the hexamer **1** are described for a number of each *S*- and *R*-asymmetric carbon atoms as follows: (*S*,*S*,*S*,*S*,*S*,*S*)-**1** [abbreviated as (S_6)-**1**], (*S*,*S*,*S*,*S*,*S*,*R*)-**1** [abbreviated as (S_5,*R*)-**1**], (*S*,*S*,*S*,*S*,*R*,*R*)-**1** [abbreviated as (S_4,R_2)-**1**], (*S*,*S*,*S*,*R*,*R*,*R*)-**1** [abbreviated as (S_3,R_3)-**1**], (*S*,*S*,*R*,*R*,*R*,*R*)-**1** [abbreviated as (S_2,R_4)-**1**], (*S*,*R*,*R*,*R*,*R*,*R*)-**1** [abbreviated as (*S*,R_5)-**1**], and (*R*,*R*,*R*,*R*,*R*,*R*)-**1** [abbreviated as (R_6)-**1**]. The isomer of the tetramer **3** is also shown in the same manner.

[13] The isomer ratio of the stochastic racemic mixture of the hexamer **1** was (S_6)/(S_5,*R*)/(S_4,R_2)/(S_3,R_3)/(S_2,R_4)/(*S*,R_5)/(R_6)-**1** = 1:6:15:20:15:6:1. The ratio of seven isomers of compound **1** (except for the isomers caused by the asymmetric silicon atoms and substitution pattern of (*S*)- and (*R*)-pyrimidyl alkanols on the branches) can be analyzed using HPLC on a chiral stationary phase.