In this study, we have generated DNA–silica minerals containing a Cu(ligand) complex and evaluated their utility in asymmetric synthesis. Cu(dmbpy)/DNA–silica mineral could be applied successfully to the Diels–Alder reaction and reused readily for 10 cycles without loss of enantioselectivity.

DNA, the ubiquitous biopolymer that exists in all living organisms on earth, is nowadays exploited in a wide range of research fields from biology as genetic information storage materials to materials science as a useful building block. DNA has received attention as an attractive chiral source for asymmetric synthesis because of its unique helical chirality, chemical stability, and water solubility. In 2005, Feringa and Roelfes introduced a new concept of biohybrid catalysis based on catalytically active metal complexes, binding ligands, and DNA, the so-called DNA-based hybrid catalysts. Since then, DNA-based asymmetric catalysis has been recognized and actively studied as an environmentally friendly strategy for the synthesis of enantiomerically pure compounds. Our group is exploring the potential of DNA for asymmetric synthesis. We have developed asymmetric intramolecular Friedel–Crafts alkylations using a self-assembled DNA hybrid catalyst. To understand the structural and mechanistic features of DNA-based asymmetric catalysis, we have devised a systematic DNA hybrid catalyst based on the direct incorporation of an intrastand bipyridine ligand into the DNA phosphate backbone and demonstrated its application to the asymmetric intramolecular Friedel–Crafts alkylations. We have also focused on a heterogeneous reaction system, which has a number of practical benefits, such as the easy separation of products/catalysts by filtration and recyclability of catalysts. In 2013, we devised a method to immobilize DNA on a silica support based on the electrostatic interaction between its anionic phosphate backbone and cationic quaternary ammonium-functionalized silica, and demonstrated that this supported DNA could be reused as a chiral source in the Cu(II)-catalyzed Diels–Alder reaction in water. This is the first example of a recyclable solid-supported DNA applied to asymmetric catalysis. Benedetti et al. reported that a cellulose-supported DNA-based hybrid catalyst could catalyze Friedel–Crafts alkylations and Michael additions with good-to-high enantioselectivities. They also demonstrated continuous-flow processes using their cellulose-supported DNA-based hybrid catalyst. Despite this notable advance, heterogeneous DNA hybrid catalysts have rarely been employed for asymmetric synthesis. Considering the high industrial relevance of heterogeneous catalysis, merging DNA-based asymmetric synthesis and heterogeneous catalysis needs further investigation.

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Copper-containing DNA–Silica Mineral Complexes for the Asymmetric Diels–Alder Reaction

Figure 1. Preparation of metal(ligand)-containing DNA–silica minerals. The picture shows Cu(dmbpy)/DNA–silica minerals.

Figure 2. Biding ligands for copper-containing DNA–silica minerals

We first prepared standard Mg/DNA–silica mineral by following the procedures established by Che et al., in which salmon testes DNA (st-DNA) was used as a readily available DNA source (see SI). To examine the utility of DNA–silica minerals in DNA-based asymmetric synthesis, we performed Cu(II)-catalyzed asymmetric Diels–Alder reactions with azachalcone (1a) and cyclopentadiene (2) in the presence of 15 mg of DNA–silica mineral in 20 mM MOPS buffer solution (300 µl, pH 6.5) at 5 °C for 1 day. The enantioselectivity and conversion were determined by HPLC analysis based on the literature.
Table 1. Asymmetric Diels–Alder reactions withaza-chalcone \( \textbf{1a} \) and cyclopentadiene \( \textbf{2} \) in the presence of metal/DNA–silica minerals.

<table>
<thead>
<tr>
<th>entry</th>
<th>metal complex</th>
<th>enantioselectivity (%) ee(^a)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgCl(_2)</td>
<td>–</td>
<td>trace</td>
</tr>
<tr>
<td>2(^a)</td>
<td>MgCl(_2)</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>Cu(NO(_3))(_2)</td>
<td>10</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Cu(dmbpy)</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>Cu(5,6-dmp)</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>Cu(php)</td>
<td>19</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>Cu(dpq)</td>
<td>13(^c)</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>Cu(dpz)</td>
<td>12</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>Cu(terpy)</td>
<td>9(^c)</td>
<td>23</td>
</tr>
</tbody>
</table>

\(^a\)Experiments were conducted using 1 \( \mu \text{mol} \) of aza-chalcone, 24 \( \mu \text{mol} \) of cyclopentadiene, and 15 \( \mu \text{g} \) of Cu(L, L = ligand)/DNA–silica mineral at 5 °C in 20 mM MOPS buffer solution (pH 6.5) for 1 day unless otherwise noted. The conversion, enendo/exo selectivities, and enantioselectivities were determined by chiral HPLC analysis. All of the reactions gave enendo/exo selectivities higher than 96%. Therefore, the enantioselectivities in this paper are only for the endo isomer. Results represent the average value of more than two experiments. \(^b\)Preincubated reaction suspension 15 \( \mu \text{mol} \) of Cu(dmbpy) with 15 \( \mu \text{g} \) of Mg/DNA–silica mineral in 20 mM MOPS buffer solution (300 \( \mu \text{l} \), pH 6.5) at 5 °C for 1 h. \(^c\) enantiomer of Diels–Alder product was obtained.

A reaction with only Mg/DNA–silica mineral showed almost no conversion. Interestingly, when we used preincubated reaction suspension that was prepared by mixing 15 \( \mu \text{mol} \) of Cu(dmbpy) with 15 \( \mu \text{g} \) of Mg/DNA–silica mineral in 20 mM MOPS buffer solution (300 \( \mu \text{l} \), pH 6.5) at 5 °C for 1 h, the Diels–Alder adduct was obtained in moderate conversion and good enantioselectivity (68% conversion and 84% ee, entry 2 in Table 1). This promising result prompted us to investigate DNA–silica mineralization using Cu(L)-containing DNA complexes in place of Mg(II) ions. We generated DNA–silica complexes with a variety of Cu(L) complexes as follows: 1.6 mM of \( N \)-trimethoxysilylpropyl-N,N,N-trimethylamonium chloride (TMAPS) and 4.3 mM of tetraethyl orthosilicate (TEOS) were added to the prepared Cu(L)/DNA solution and mixed for 30 min. Then, the solution was left for 3 days at RT. As the Cu(L) complexes used for the mineralization, various pale-colored powders were obtained and examined in the Cu(II)-catalyzed asymmetric Diels–Alder reactions as shown in Table 1. The standard reaction conditions were determined as follows: 1 \( \mu \text{mol} \) aza-chalcone \( \textbf{1a} \) (0.5 M solution in acetonitrile) and 24 \( \mu \text{mol} \) cyclopentadiene \( \textbf{2} \) were added to 20 mM MOPS buffer solution (300 \( \mu \text{l} \), pH 6.5) including 15 \( \mu \text{g} \) of Cu(L)/DNA–silica mineral and mixed by continuous rotation at 5 °C for 1 day. Cu(II)/DNA–silica mineral without a bidentate ligand gave the product in low enantioselectivity (entry 3 in Table 1). To our delight, when we performed the reaction with Cu(dmbpy)/DNA–silica mineral, Diels–Alder product was obtained with excellent enantioselectivity (up to 99% ee), almost full conversion (97%), and good reproducibility (entry 4 in Table 1, Table S1). As a result, we found that different enantioselectivities and conversions of Diels–Alder adducts were observed depending on the Cu(L) complexes comprising the DNA–silica mineral. Although a Cu(dmbpy)/DNA–silica mineral afforded the highest enantioselectivity of the product as previously established homogeneous DNA-based Cu(II)-catalyzed Diels–Alder reactions,\(^4\) a general tendency between the Cu(L)/DNA–silica minerals and the observed enantioselectivities was not consistent with the results by homogeneous DNA-based Cu(II)-catalyzed Diels–Alder reactions. This suggests that the chiral microenvironment in heterogeneous Cu(L)/DNA–silica minerals might be different from that in homogeneous Cu(L)/DNA duplexes in water. We also cannot exclude the possibility that various chiral environments surrounding DNA and inside DNA affect the outcome of the reactions.\(^5\)

Table 2. Investigation of substrate scope for the asymmetric Diels–Alder reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>products ee (%)(^a)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b 1f</td>
<td>( R_1 = 2 )-pyridyl, ( R_2 = \text{aza} )-chalcone ( \textbf{1a} )</td>
<td>85</td>
</tr>
<tr>
<td>1c 1f</td>
<td>( R_1 = 2 )-pyridyl, ( R_2 = p )-ChCl ( \textbf{1a} )</td>
<td>86</td>
</tr>
<tr>
<td>1d 1f</td>
<td>( R_1 = 2 )-pyridyl, ( R_2 = p )-ClC ( \textbf{1a} )</td>
<td>95</td>
</tr>
<tr>
<td>1e 1f</td>
<td>( R_1 = 2 )-pyridyl, ( R_2 = p )-BrC ( \textbf{1a} )</td>
<td>98</td>
</tr>
<tr>
<td>1f 1f</td>
<td>( R_1 = 2 )-pyridyl, ( R_2 = o )-Ch ( \textbf{1a} )</td>
<td>97</td>
</tr>
</tbody>
</table>

\(^a\)Experiments were conducted using 1 \( \mu \text{mol} \) of aza-chalcone, 24 \( \mu \text{mol} \) of cyclopentadiene, and 15 \( \mu \text{g} \) of Cu(dmbpy)/DNA–silica minerals at 5 °C in 20 mM MOPS buffer (pH 6.5) for 1 day unless otherwise noted. The conversion, enendo/exo selectivities, and enantioselectivities were determined by chiral HPLC analysis. All of the reactions gave enendo/exo selectivities higher than 96%. Therefore, the enantioselectivities in this paper are only for the endo isomer. Results represent the average value of more than two experiments. The reactions were performed at RT.

Based on the results from Table 1, the scope of aza-chalcones, \( \textbf{1b} \)–\( \textbf{1f} \), was investigated under standard reaction conditions. Aza-chalcones having \( o \)-chlorophenyl group (\( \textbf{1b} \)) and \( p \)-nitrophenyl group (\( \textbf{1d} \)) gave the desired Diels–Alder products with high enantioselectivity (85% and 99% ee, respectively) and almost full conversion (entries 1 and 4 in Table 2). The substituents on the aza-chalcone such as \( p \)-bromophenyl (\( \textbf{1c} \)) and \( p \)-methoxyphenyl group (\( \textbf{1d} \)) required ambient temperature to increase the conversion of substrates. Unfortunately, in the case of aza-chalcones having \( p \)-methoxyphenyl group (\( \textbf{1b} \)), a significant decrease of
entantioselectivity was observed (35% ee, entry 3, Table 2). Regarding the 2-acyl pyridyl moiety onaza-chalcone, the 2-acyl-N-methylimidazoyl moiety could replace the 2-acyl pyridyl group and afforded the desired product with 81% ee and 97% conversion (entry 5, Table 2). When we performed the reaction with chalcone instead ofaza-chalcone, almost no conversion was observed. The bidentate substrates are crucial for the reaction progress.

Table 3. Intramolecular Friedel–Crafts alkylation using Cu(L)/DNA–silica minerals.

<table>
<thead>
<tr>
<th>ligand</th>
<th>dmbpy 5,6-dmp</th>
<th>dpb</th>
<th>dpdz</th>
<th>terpy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ee (%)</td>
<td>43</td>
<td>69</td>
<td>18</td>
<td>37</td>
</tr>
<tr>
<td>yield (%)</td>
<td>22</td>
<td>25</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>95</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Experiments were conducted using 1 µmol tethered indole substrate and 15 mg Cu(L)/DNA–silica minerals at RT in 20 mM MOPS buffer (pH 6.5) for 5 h unless otherwise noted. The yields and entantioselectivities were determined by chiral HPLC analysis. Results represent the average value of more than two experiments.

To verify the usability of Cu(L)/DNA–silica minerals, intramolecular Friedel–Crafts alkylation were conducted with various Cu(L)/DNA–silica minerals (Table 3). The best result (69% ee) was obtained with Cu(5,6-dmp)/DNA–silica mineral and this is comparable to the previous result from homogeneous DNA-based intramolecular Friedel–Crafts alkylation. Like the Diels–Alder reactions, different entantioselectivities of the products were obtained depending on the Cu(L) complexes comprising DNA–silica minerals. Although the yields of the product were generally low, these results demonstrate the potential application for Cu(L)/DNA–silica minerals for DNA-based asymmetric synthesis. Considering the amount of Cu(dmbpy) complex and availability of Cu(dmbpy)/DNA–silica minerals, we performed Cu(II)-catalyzed Diels–Alder reaction at preparative scale. Aza-chalcone 1a (50.2 mg; 0.24 mmol) and cyclopentadiene 2 (5.6 mmol) were added to 20 mM MOPS buffer solution (20 ml, pH 6.5) in the presence of 70 mg Cu(dmbpy)/DNA–silica mineral containing less than 7 mol% of Cu(dmbpy) complex at 5 °C. After 3 days, 50.0 mg of Diels–Alder adduct was obtained as a mixture of the endo and exo isomers (endo/exo = 32:1) in 76% yield with 91% ee for the endo isomer. Results represent the average value of more than two experiments.

In conclusion, we have prepared Cu(dmbpy)/DNA–silica minerals and successfully applied them in the Cu(II)-catalyzed asymmetric Diels–Alder reactions with excellent enantioselectivity and almost full conversion (up to 99% ee and 99% conversion). A variety of DNA–silica minerals containing Cu(ligand) complexes could be generated using a straightforward method and they are stable in air and water. In addition, Cu(dmbpy)/DNA–silica mineral was readily reusable up to 10 cycles without loss of enantioselectivity. Although further study is needed to clarify the chiral induction mechanism of Cu(L)/DNA–silica mineral, this proof of concept study shows that metal-containing DNA–silica minerals can serve as durable heterogeneous biobridged catalysts for asymmetric synthesis. We are currently developing new DNA–silica minerals using various metal complexes besides Mg(II) ions and Cu(II) ions for DNA-based asymmetric synthesis.

Supporting Information is available on http://dx.doi.org/10.1246/cl.*****

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Conflict of interest statement. None declared.

References and Notes
Several heterogeneous metal/DNA catalysts and metal nanoparticles supported on DNA have been developed for the chemical reactions such as oxidation, hydrogenation and Suzuki-Miyaura coupling reactions (ref. 27). Nanoparticles supported on DNA have been developed for the enantioselectivities of the desired products. We are under study to investigate the effect of Cu(L) complexes on the helicity of Cu(L)/DNA-silica complexes.
In this study, we have generated DNA-silica minerals containing a Cu(ligand) complex and evaluated their utility in asymmetric synthesis. Cu(dmbpy)/DNA–silica mineral could be applied successfully to the Diels–Alder reaction and reused readily for 10 cycles without loss of enantioselectivity.

Copper-containing DNA–Silica Mineral Complexes for the Asymmetric Diels–Alder Reaction

Sohei Sakashita,¹ Soyoun Park,*¹ and Hiroshi Sugiyama*¹,²

Cu(dmbpy)/DNA-silica mineral

easy to prepare
stable & recyclable

up to 97% conversion
endo / exo > 40 : 1
up to 99% ee for endo
Supporting Information

Copper-containing DNA–Silica Mineral Complexes for the Asymmetric Diels–Alder Reaction

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Materials
Deoxynucleic Acid from salmon testes (st-DNA) was purchased from Aldrich and used as received. N-trimethoxysilylpropyl-N,N,N-trimethylammonium chloride (TMAPS) and tetraethyl orthosilicate (TEOS) were purchased from TCI and used as received. All other chemicals and solvents were purchased from Sigma-Aldrich Chemicals Co., Wako Pure Chemical Ind. Ltd., TCI, and Nacalai Chemical Co. Water was deionized (specific resistance of > 18.0 MW cm at 25 °C) by a Milli-Q system (Millipore Corp.). Aza-chalcone 1a was synthesized as reported procedure.1 Cyclopentadiene was prepared by cracking dicyclopentadiene. Substrate 4 for intramolecular Friedel-Crafts alkylations was synthesized as previously reported.4

Methods
For the synthesis of substrates and the preparative-scale reactions, NMR spectra were obtained on a JEOL JNM ECA-600 spectrometer operating at 600 MHz for 1H NMR and in CDCl3 unless otherwise noted. Flash Column chromatography was performed employing WakoGel
60N (63–212 mesh, Wako). Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates from Silica gel 70 PF254 (Wako Pure Chemical Ind. Ltd.). Enantiomeric excess (ee) was determined by HPLC analysis (Chiralcel OD-H, AD-H) using UV-detection. Detail HPLC conditions were shown in the previous study.\(^2\) DNA concentration was measured by Nanodrop ND-1000 spectrophotometer. Rotary mixing of the reaction suspension was performed by Intelli-Mixer RM-2 (Elmi). Eyela FDU-1100 was used for the freeze-drying.

**Preparation of Cu(ligand)/DNA–silica minerals**

43.2 mg of st-DNA was solved in the 33 ml of deionized water. To st-DNA solution, 0.023 mmol of (20 mM Cu(ligand) solution, 840 µl) was added. After mixing well, 180 µl of \(N\)-trimethoxysilylpropyl-\(N,N,N\)-trimethylammonium chloride (TMAPS), 300 µl of tetraethyl orthosilicate (TEOS) were added to the solution. After the mixing for 1 h at 5 \(^\circ\)C, the solution was left to stand at ambient temperature for 3 days. Cu(ligand)/DNA–silica mineral was collected by centrifugation (13,000 rpm for 4 min), then washed by 10 ml of deionized water at 3 times, and freeze-dried. In this procedure, 60–100 mg of the Cu(ligand)/DNA–silica minerals was usually obtained as the powder.
General Procedure for the Diels-Alder reactions using Cu(ligand)/DNA–silica minerals

The reaction was conducted in 1.5 ml of eppendorf tube. 15 mg of Cu(ligand)/DNA–silica mineral was added to 300 µl of 20 mM MOPS buffer (pH 6.5), and mixed by continuous rotation at 5 °C for 1 h. After 1 h, 1 µmol of aza-chalcone 1a (0.5 M solution in acetonitrile) and 24 µmol of cyclopentadiene 2 (2 µl) were added to the solution and mixed by continuous rotation at 5 °C for 1 day. The products were extracted with diethyl ether at 3 times and the solvent was removed under reduced pressure. The e.e. of the product was determined on a Daicel Chiralcel OD-H column with a solvent mixture, hexane: 2-propanol = 95:5, under a flow rate of 0.5 mL/min. The HPLC conditions of other substrates were determined as the previously reported study.1-4

Investigation of DNA leaching from Mg/ DNA–silica mineral

15 mg of Mg/DNA–silica mineral was added to the 300 µl of 20 mM MOPS buffer (pH 6.5) in 1.5 ml of eppendorf tube. Then suspension was set to rotary mixer and mixed by continuous rotation at 5 °C. In order to monitor DNA concentration by leaching from Mg/DNA–silica mineral, we measured the absorbance intensity at 260 nm in supernatant liquid after the centrifugation (13,000 rpm for 1 min).

Figure S1. DNA concentration in MOPS buffer solution in the presence of Mg/DNA–silica mineral.

The blue dots represent DNA concentration in MOPS buffer solution in the presence of Mg/DNA–silica mineral. At the beginning of the experiment, the absorbance intensity at 260 nm in supernatant liquid indicated 6.0 ng/µl of DNA concentration. After 1 day mixing, the concentration of DNA concentration was observed up to 9.7 ng/µl. Based on this result, we...
conducted the Diels-Alder reaction using 9.7 ng/µl st-DNA solution containing 3 mol% of Cu(dmbpy). As a result, the desired product was obtained in 28% ee and low conversion.

**Reproducibility of Cu(dmbpy)/DNA–silica mineral**

For the reproducibility investigation, 5 samples of Cu(dmbpy)/DNA–silica minerals were generated independently and examined in the Diels-Alder reaction. The reactions were conducted using 1 µmol aza-chalcone, 24 µmol cyclopentadiene, and 15 mg Cu(dmbpy)/DNA–silica minerals at 5 °C in 20 mM MOPS buffer (pH 6.5) for 1 day. As shown in the Table S1, every Cu(dmbpy)/DNA–silica mineral afforded the desired product with excellent enantioselectivities and high conversions.

<table>
<thead>
<tr>
<th>Lot number</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>5</th>
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<th>9</th>
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<th>Average value</th>
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<tbody>
<tr>
<td>ee (%)a</td>
<td>94</td>
<td>92</td>
<td>98</td>
<td>87</td>
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<td>94</td>
<td>97</td>
<td>93</td>
<td>99</td>
<td>95 ± 2.5</td>
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<tr>
<td>Conversion (%)a</td>
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<td>98</td>
<td>96</td>
<td>86</td>
<td>88</td>
<td>85</td>
<td>91</td>
<td>87</td>
<td>95</td>
<td>95</td>
<td>92 ± 4.9</td>
</tr>
</tbody>
</table>

*Table S1. Reproducibility of Cu(dmbpy)/DNA–silica mineral*

**Preparative scale Diels-Alder reaction**

The reaction was conducted in 50 ml of conical tube. 70 mg of Cu(ligand)/DNA–silica mineral was added to 20 ml of 20 mM MOPS buffer (pH 6.5), and mixed by continuous rotation at 5 °C for 1 h. After 1 h, 0.24 mmol of aza-chalcone 1a (0.8 M solution in acetonitrile) and 5.8 mmol of cyclopentadiene 2 were added to the solution and mixed by continuous rotation at 5 °C for 3 days. The reaction mixture was extracted with diethyl ether at 3 times and the solvent was
removed under reduced pressure. The residue was purified by silica gel preparative TLC with Hexane/EtOAc = 3:1 to afford the compound 3a as a colorless oil (50.0 mg, 76% yield, endo/exo = 32:1, 91% ee for endo isomer). The ee and endo/exo ratio of the product were determined on a Daicel Chiralcel OD-H column with a solvent mixture, hexane:2-propanol = 95:5, under a flow rate of 0.5 mL/min.

**Procedure for reusability of Cu(dmbpy)/DNA–silica mineral**

The Diels-Alder reactions were conducted as above-mentioned in general procedure. After the extraction with diethyl ether, Cu(dmbpy)/DNA–silica mineral was recovered by centrifugation and reused for the next reaction with 300 µl of fresh MOPS buffer solution (20 mM, pH 6.5).

**References**


