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A Chiral Bis(oxazoline) Ligand Embedded into Polysiloxane Gel: Application to a Reusable Copper Catalyst for Asymmetric Cyclopropanation

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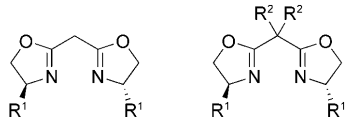
Metal-catalyzed asymmetric reactions are one of the most efficient tools for the production of optically active molecules.[1] Rational design of chiral ligands and proper choice of transition metals enable one to produce desired molecules in high yields with high enantioselectivity. However, the separation, recovery, and reuse of chiral ligands are problems to be solved in considering the cost of the catalyst, while those of metallic species from products are important from an environmental point of view. Immobilization of chiral transition-metal complexes to polymer supports or on a solid surface is one of the solutions to these problems.[2] Among them, cross-linked polydimethylsiloxanes (PDMS) are known to behave as efficient carrier materials for physically entrapped transition-metal complexes owing to their advantages on thermal stability, rapid transportation of organic molecules through the siloxane matrix, and effective stabilization of catalitically active species.[3] However, molecular catalysts supported on the PDMS resin have not been fully investigated in organic synthesis. A major problem is leaching of the occluded metal species to organic solvents; reactions are usually carried out in aqueous or alcoholic media to avoid the metal leaching.

We have recently established a convenient and effective method to synthesize polysiloxane gels containing transition-metal species, [M]@Si, by metal-catalyzed cross-linking of polymethylhydrosiloxane (PMHS).[4,5] Our new method has several advantages over the conventional way to prepare metal-occluding PDMS. First, cross-linking of PMHS is achieved with ease by transition-metal-catalyzed hydrosilylation of α,ω-dienes or dehydrogenative silylation of α,ω-diols; the cross-linking is accompanied by effective entrapment of the catalyst species (M^1). The [M^1]@Si, where M^1 = Pt and Ru, is useful for the reusable catalysts for promoting isomerization of alkenes[5a] and for hydrogenation of nitroarenes[5b] without metal leaching in common organic solvents. Second, various α,ω-dienes and α,ω-diols can be used as a cross-linker; this makes it possible to introduce functional groups which potentially act as a ligand for the second transition metal (M^2) as a component of the gel. We have recently synthesized a gel including a 2,2′-bipyridine unit in the cross-linker, [bipy][Pt]@Si, which is followed by treatment with CuCl to form [CuCl(bipy)][Pt]@Si.[5c] The copper(I) species in the gel catalyzed the atom-transfer radical cyclization of *N*-allyltrichloroacetamides without leaching of both Cu and Pt, and the catalyst, [CuCl(bipy)][Pt]@Si, was reusable. Success of using [CuCl(bipy)][Pt]@Si prompted us to examine introduction of chiral amines to the cross-linker and its application to asymmetric synthesis. Herein, we wish to report the first results along this line, in which a 2,2′-methylenebis(oxazoline) unit[6] (Box; Scheme 1) is introduced to the cross-linker to form [Box][Pt]@Si. The resulting gel, [Box][Pt]@Si, is treated with $Cu(OTf)_2$ to give [$Cu(OTf)_2$(Box)][Pt]@Si. Utility of [$Cu(OTf)_2$(Box)][Pt]@Si is demonstrated by Cu-catalyzed asymmetric cyclopropanation of alkenes with L-menthyl diazoacetate.[7]



Scheme 1. Chiral bis(oxazoline) (Box) ligands.

The reaction of (*S,S*)-*t*Bu_2-Box, methylenebis(oxazoline) bearing *tert*-butyl groups at the 4,4′-positions, with allyl bromide in the presence of sodium hydride afforded a (*S,S*)-*t*Bu_2-Box ligand with diallyl groups on the bridge carbon (**1**: (*S,S*)-*t*Bu_2-DABox).[7d,8] Preparation of a gel to give [(*S,S*)-*t*Bu_2-DABox][Pt]@Si was carried out by treatment of **1**

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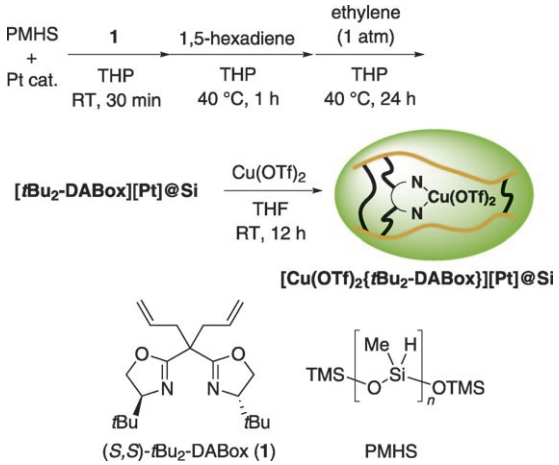
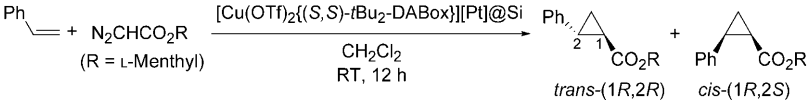
(0.05 mmol) with PMHS (Si-H = 2 mmol) in the presense of Karstedt's catalyst[9] ([Pt] = 5 μmol) in tetrahydropyran (0.5 mL) at room temperature for 30 minutes. Subsequent addition of 1,5-hexadiene (180 μL, 1.5 mmol) at 40 °C for 1 hour resulted in further cross-linking of PMHS to give the polysiloxane gel as a yellow solid. NMR analysis of the solution suggested that all of the (*S,S*)-*t*Bu$_2$-DABox and a part of charged 1,5-hexadiene were linked to the siloxane chain. Solid-state ^{29}Si and ^{13}C NMR analyses revealed that about 75% (3 mmol) of the Si-H groups in the PMHS used were converted into the Si–C moieties, and 25% of them remained unreacted. The remaining Si-H groups were converted into Si-Et moieties by subsequent treatment with ethylene (1 atm) at 40 °C for 12 hours (remaining Si–H groups were below 5%).[8,10] The gel contained about 10% of the alkenyl moieties and 25% of the ethyl groups, which do not contribute to cross-linking the siloxane chains; thus, the cross-linking density of the formed gel was calculated to be 65%.



Scheme 2. Preparation of [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si.

Treatment of [(*S,S*)-*t*Bu$_2$-DABox][Pt]@Si with Cu(OTf)$_2$ (0.02 mmol) in THF at room temperature under an argon atmosphere resulted in generation of Cu(OTf)$_2$[(*S,S*)-*t*Bu$_2$-DABox] species in the gel (Scheme 2). The color of the gel gradually turned from yellow to light green. After 12 hours, the gel was washed with THF and dried under vacuum to afford [Cu(OTf)$_2$ {(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si as a dry gel. ICP-MS analysis showed that the THF solution contained 228 μg of copper; which means that 82% (1.28 mg, 16.4 μmol) of the charged Cu(OTf)$_2$ was entrapped in the gel.[8]

Table 1. Asymmetric cyclopropanation of styrene with L-menthyl diazoacetate catalyzed by [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si.[a]



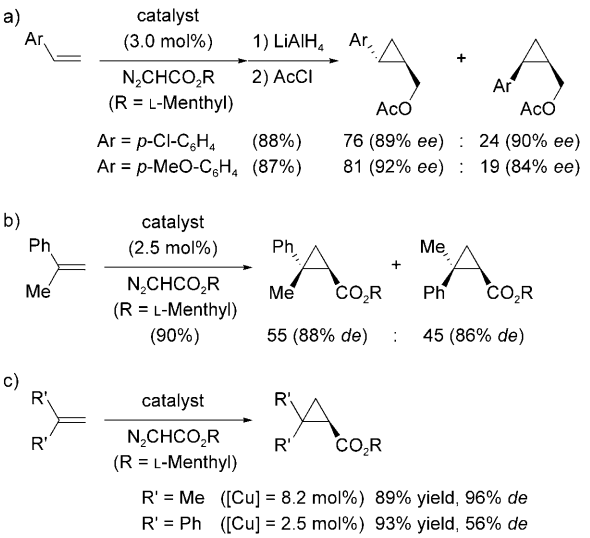
Entry	Catalyst [mol%]	Styrene [equiv]	Yield [%]	*trans*/*cis*[b]	*de* (*trans*) [%][b]	*de* (*cis*) [%][b]
1	8.2	10	55	82:18	95	96
2	1.6	10	50	85:15	96	89
3	4.2	50	75	86:14	92	82
4[c]	2.5	100	98	81:19	92	88
5[d]	2.5	100	99	82:18	97	96
6[e]	2.5	100	ca. 5	59:41	<1	<1

[a] All reactions were carried out using L-menthyl diazoacetate (0.2 mmol) in dichloromethane (2 mL) at ambient temperature for 12 h without stirring. [b] Determined by GLC analysis. [c] For 5 h. [d] 1.1:1 mixture of *t*Bu$_2$-Box/Cu(OTf)$_2$ was used as a catalyst (homogeneous system). [e] [(*S,S*)-*t*Bu$_2$-DABox][Pt]@Si was used as a catalyst.

Application of [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si to catalytic asymmetric cyclopropanation was examined as a representative example of its catalysis.[11] In a flask was placed [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si (1.6–8.2 mol% Cu), to which were added styrene (10–100 equivalent to L-menthyl diazoacetate), CH_2Cl_2 (1 mL), and a CH_2Cl_2 solution of L-menthyl diazoacetate (0.2 mmol/2 mL of CH_2Cl_2) in that order. The resultant mixture was allowed to stand at room temperature without stirring. After the reaction was complete, the mixture was filtered through a pad of cotton and the solvent was removed under reduced pressure. The [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si catalysts were recovered as a dry gel on a cotton pad, while *trans*- and *cis*-2-phenylcyclopropane-1-carboxylates were obtained from the filtrate. As shown in Table 1, yields of L-menthyl-2-phenylcyclopropane-1-carboxylates were dependent on the amount of styrene used. This is due to formation of by-products such as cyclopropane-1,2,3-tricarboxylate,[12] and di-L-menthyl maleate and fumarate; these are derived from decomposition of L-menthyl diazoacetate. Although use of 10–50 equivalents of styrene per equivalent diazoacetate cannot suppress the by-product formation (Table 1, entries 1–3), addition of 100 equivalents of styrene to the diazoacetate in the presence of the gel catalyst, with the amount of Cu at 5 μmol (S/C = 40), gave the desired cyclopropane as a 4:1 mixture of *trans* and *cis* isomers in 98% yield. The diastereomeric excesses of the products determined by GLC analysis were 92% *de* (*trans* isomer) and 88% *de* (*cis* isomer), respectively (Table 1, entry 4). A controlled experiment, in which a homogeneous reaction with Cu(OTf)$_2$(*t*Bu$_2$-Box) catalyst prepared in situ from Cu(OTf)$_2$ and *t*Bu$_2$-Box (1.1 equiv per equiv Cu) was used instead of the gel catalyst under the same reaction conditions as above (Table 1, entry 5), showed that the gel catalyst gave slightly lower *de* values than the homogeneous catalyst. This may be ascribed to contamination of the cyclopropanation catalyzed by a platinum species remaining in the gel. A control experiment performed under the same conditions as the reaction of L-menthyl diazoacetate with styrene catalyzed by [(*S,S*)-*t*Bu$_2$-

DABox][Pt]@Si revealed that a 6:4 *trans*/*cis* mixture of the cyclopropane was formed in racemic form in lower than 5% yield (Table 1, entry 6).

Asymmetric cyclopropanation of other alkenes was also achieved with [Cu(OTf)$_2$\{(*S,S*)-*t*Bu$_2$-DABox\}][Pt]@Si as shown in Scheme 3. The reaction of either substituted styrene derivatives (Scheme 3a) or α-methylstyrene (Scheme 3b) with L-menthyl diazoacetate was similar to that of styrene shown in Table 1, entry 4, in that the desired product was obtained as a mixture of *cis* and *trans* isomers in high yields with greater than 86% *de*. Since the cyclopropanation of isobutene was slower than that with the homogeneous system, a larger amount of the catalyst was necessary to obtain the product. Using 8.2 mol% of the gel catalyst, the reaction gave the product with over 96% *de* in 89% yield (Scheme 3c; R′=Me). Although the cyclopropanation of 1,1-diphenylethylene, which is more sterically hindered than isobutene and α-methylstyrene, with L-menthyl diazoacetate proceeded smoothly to give the product with high *de* using homogeneous Cu(OTf)$_2$(*t*Bu$_2$-Box) catalyst,[13] the gel catalyst gave the product in good yield but with insufficient diastereomeric excess (56% *de*) (Scheme 3c; R′=Ph). In the reaction with more sterically hindered trisubstituted 2,5-dimethyl-2,4-hexadiene, dimerization of L-mentyl diazoacetate was preceded by the cyclopropanation to give only a trace amount of the cyclopropanes. These results may suggest that the polysiloxane gel provides a smaller reaction cavity for the asymmetric cyclopropanation reaction, which gives no problem for the reaction with sterically less-hindered alkenes, but is unfavorable for the more hindered substrates.



Scheme 3. [Cu(OTf)$_2$\{(*S,S*)-*t*Bu$_2$-DABox\}][Pt]@Si-catalyzed cyclopropanation of other alkenes with L-menthyl diazoacetate.

It is of great advantage that siloxane gels encapsulating the molecular catalysts are facilely separated from the product and reusable. In a typical example, isobutylene and L-menthyl diazoacetate (0.2 mmol) were treated with [Cu(OTf)$_2$\{(*S,S*)-*t*Bu$_2$-DABox\}][Pt]@Si (Cu=14.6 μmol, 7.3 mol%) as described in Scheme 3. After a solution containing the desired product was separated by filtration, [Cu(OTf)$_2$\{(*S,S*)-*t*Bu$_2$-DABox\}][Pt]@Si was recovered as a solid and subjected to further runs of cyclopropanation. As shown in Table 2, L-menthyl-2,2-dimethylcyclopropane-1-carboxylate was obtained in good yields (77–92%) with high stereoselectivity (86–92% *de*). A small amount of metal leaching was observed in each run; ICP-MS analysis revealed that the crude product in each run contained 16–38 μg of copper species: this corresponds to about 2–4% of the copper moiety charged at the first run.

Table 2. Recycling experiments in asymmetric cyclopropanation of isobutylene with L-menthyl diazoacetate.[a]

Run	Cu in the crude [μg][b]	Yield [%]	*de* [%][c]
1st	38	88	86
2nd	21	92	87
3rd	22	87	89
4th	16	82	88
5th	23	77	92

[a] All reactions were carried out using L-menthyl diazoacetate (0.2 mmol) and [Cu(OTf)$_2$\{(*S,S*)-*t*Bu$_2$-DABox\}][Pt]@Si ([Cu]=7.3 mol%) in dichloromethane (2 mL) at ambient temperature for 24 h without stirring. [b] Determined by ICP-MS analysis. [c] Determined by GLC analysis.

In summary, we successfully synthesized polysiloxane gels containing a chiral bis(oxazoline) ligand, [(*S,S*)-*t*Bu$_2$-DABox][Pt]@Si. Treatment of [(*S,S*)-*t*Bu$_2$-DABox][Pt]@Si with Cu(OTf)$_2$ gave [Cu(OTf)$_2$\{(*S,S*)-*t*Bu$_2$-DABox\}][Pt]@Si, which was proved to be a reusable chiral catalyst for cyclopropanation of alkenes with L-menthyl diazoacetate. Of particular importance is that the gel catalyst was able to be recovered by filtration, and was reusable five times. Neither loss of the catalytic activity nor decrease of asymmetric induction was observed in the recycling experiments. This system is advantageous over the immobilized Cu/Box catalysts for the asymmetric cyclopropanation that were reported previously, in that the current method for immobilization is the easiest. From the viewpoint of catalytic activity and asymmetric induction, the present method is comparable to the most effective method reported in the literature in the asymmetric cyclopropanation of styrene and isobutene.[7g] Although the asymmetric induction of 1,1-diphenylethylene was less effective than that with the catalyst reported in reference [7g], it is interesting that the result first provided the finding to make us assume that polysiloxane gel may provide a smaller reaction cavity for catalysis. These present results have thus opened a novel access to immobilized chiral catalysts, "chiral polysiloxane gel catalysts", which are facilely prepared by platinum-catalyzed hydrosilylation of α,ω-diolefins having a chiral functional group with PMHS. Further investigation on the preparation and catalysis of "chiral polysiloxane gel catalysts" is actively in progress.

Experimental Section

All reactions were carried out under a nitrogen or argon atmosphere. Anhydrous solvents (THF, hexane, and dichloromethane) were purchased from Kanto Chemical Co., Ltd., and used as received. THP was purchased from Tokyo Chemical Industry Co., Ltd., and distilled under an inert atmosphere from sodium/benzophenone prior to use. Diethylmalonimidate hydrochloride, (L)-*tert*-leucinol, allyl bromide, and 1,5-hexadiene were purchased from Tokyo Chemical Industry Co., Ltd. Karstedt's catalyst in 0.1 M xylene solution was purchased from Aldrich Chemical Co. Sodium hydride was purchased from Kishida Chemical Co., Ltd. Polymethylhydrosiloxane (PMHS, $n=25$) was purchased from AZmax Co. Ltd. ^{1}H, ^{13}C, and ^{29}Si NMR spectra were measured on JEOL ECA 400 (396 MHz and 400 MHz) and ECA 600 (600 MHz) spectrometers. Chemical shifts for ^{1}H NMR are described in parts per million downfield from tetramethylsilane as an internal standard ($\delta=0$ ppm) in $CDCl_3$, unless otherwise noted. Chemical shifts for ^{13}C NMR are expressed in parts per million in $CDCl_3$ as an internal standard ($\delta=77.1$ ppm), unless otherwise noted. Chemical shifts for solid-state ^{13}C and ^{29}Si NMR spectra are described in parts per million downfield from hexamethylbenzene ($\delta=132$ ppm) and polydimethylsilane ($\delta=-34$ ppm) as an external standard. IR spectra were measured on a JASCO FT/IR-4200 spectrometer. Gas chromatography (GC) analyses were performed on a Shimadzu GC-17A gas chromatograph equipped with TC-1 and TC-17 (30 m) columns. High-performance liquid chromatography (HPLC) analyses were performed with a JASCO PU-2080 HPLC pump, UV-2075 UV/Vis detector using a Daicel CHIRALCEL OD-H column. ICP-MS analysis was performed at the Analytical Center in Institute for Materials Chemistry and Engineering, Kyushu University. Analytical thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F_{254}, layer thickness 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, and phosphomolybdic acid. L-Menthyl diazoacetate was prepared by the literature method.[14]

Typical procedure for the [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si-catalyzed cyclopropanation of L-menthyl Diazoacetate with styrene (Table 1, entry 4): To a suspension of styrene (20 mmol) and [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si catalyst ([Cu]=2.5 mol%) in dichloromethane (1 mL) was added a solution of L-menthyl diazoacetate (44.9 mg, 0.2 mmol) in dichloromethane (2 mL). After the reaction completed, the insoluble [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si catalyst was removed by filtration. The residual gel was washed with ether, and the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel chromatography gave L-menthyl-2-phenylcyclopropane-1-carboxylate[15] in 98% yield. IR (neat): $\tilde{\nu}=2953$, 2925, 2868, 1719, 1455, 1403, 1265, 1175, 1151, 754, 696 cm^{-1}; 1*R*,2*R* isomer : ^{1}H NMR (396 MHz, $CDCl_3$): $\delta=0.77$ (d, $J=6.8$ Hz, 3H, CH_3 of menthyl), 0.89 (d, $J=7.2$ Hz, 3H, CH_3 of menthyl), 0.92 (d, $J=6.8$ Hz, 3H, CH_3 of menthyl), 4.72 ppm (td, $J=10.6$, 4.3 Hz, 1H, CO_2CH); ^{13}C NMR (99.5 MHz, $CDCl_3$): $\delta=16.5$, 17.1, 20.9, 22.1, 23.5, 24.4, 26.0, 26.3, 31.5, 34.4, 41.1, 47.2, 74.5 (CO_2C), 140.4 (C_{ipso}), 173.0 ppm (C=O); 1*S*,2*S* isomer: ^{1}H NMR (396 MHz, $CDCl_3$): $\delta=$ 4.47 ppm (td, $J=11.1$, 4.3 Hz, 1H, CO_2CH); 1*R*,2*S* isomer: ^{1}H NMR (396 MHz, $CDCl_3$): $\delta=4.41$ (td, $J=10.6$, 4.3 Hz, 1H, CO_2CH); ^{13}C NMR (99.5 MHz, $CDCl_3$): $\delta=16.1$, 20.8, 22.0, 22.5, 23.3, 25.6, 26.0, 31.3, 34.2, 40.6, 46.9, 74.0 ppm (CO_2C); GLC (TC-1, 30 m, detection FID, column temp.: 200 °C), $t_R=10.6$ min (1*S*,2*R*), 10.9 min (1*R*,2*S*), 12.2 min (1*R*,2*R*), 12.7 min (1*S*,2*S*).

Recycling experiments and ICP-MS analysis of the product (Table 2): After the reaction of isobutylene and L-menthyl diazoacetate with [Cu(OTf)$_2${(*S,S*)-*t*Bu$_2$-DABox}][Pt]@Si ([Cu]=7.3 mol%) described as above, the recovered catalyst was dried under reduced pressure and subjected to a further run of cyclopropanation of isobutylene and L-menthyl diazoacetate. The copper content in the L-menthyl-2,2-dimethylcyclopropane-1-carboxylate was determined by ICP-MS analysis: the crude product obtained by the above procedure was dissolved in concentrated HCl (30 mL), and the solution was stirred at 70 °C overnight. Then the solution was diluted with 0.048 M HNO_3. The measurement was performed using this solution. The copper content was calibrated with a commercially available standard reagent (KANTO Chemical Co. INC.: copper atomic absorption standard solution, 999 mg L^{-1} Cu in HNO_3); five standard solutions, of which the Cu concentration was in a range from 10 ppb to 200 ppb, were used for calibration. L-Menthyl-2,2-dimethylcyclopropane-1-carboxylate:[16] IR (neat): $\tilde{\nu}=2953$, 2927, 2869, 1719, 1455, 1397, 1267, 1168, 1150, 1092, 830, 759 cm^{-1}; 1*R* isomer: ^{1}H NMR (396 MHz, $CDCl_3$): $\delta=0.75$ (d, $J=6.8$ Hz, 3H, CH_3 of menthyl), 0.89 (d, $J=6.8$ Hz, 3H, CH_3 of menthyl), 1.16 (d, $J=6.8$ Hz, 3H, CH_3 of menthyl), 1.46 (dd, $J=7.7$, 5.3 Hz, 1H), 4.69 ppm (td, $J=11.1$, 4.3 Hz, 1H, CO_2CH); ^{13}C NMR (99.5 MHz, $CDCl_3$): $\delta=16.5$, 19.0, 20.7, 21.6, 22.1, 22.8, 23.7, 26.5, 27.1, 27.4, 31.5, 34.4, 41.2, 47.2, 74.0 (CO_2C), 172.3 ppm (C=O); GLC (TC-1, 30 m, detection FID, column temp.: 120 to 180 °C at 1 °C min^{-1}), $t_R=17.2$ min (1*S*), 17.5 min (1*R*).

Acknowledgements

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Keywords: copper · cyclopropanation · heterogeneous catalysis · N ligands · polysiloxane gels

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