Polymer Journal (2024) 56:561–565
https://doi.org/10.1038/s41428-024-00885-x

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Selective *N*-alkylation catalyzed by polymer gels with crosslinked domains containing iridium complexes

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Received: 2 October 2023 / Revised: 14 November 2023 / Accepted: 17 December 2023 / Published online: 26 January 2024

Abstract

Polymer gel catalysts are attractive due not only to their recyclability but also to the unique reaction environment in the internal space of the network structure. Appropriate design of the nanostructure around catalytically active sites in the gel network is particularly important. In this work, we aimed to control the activity and selectivity of the iridium-catalyzed *N*-alkylation of amine substrates with alcohols by incorporating an iridium complex into the crosslinked domain (CD) nanostructure of amphiphilic gels. A variety of gels with homogeneously dispersed CD structures containing iridium complexes with various crosslinking densities were prepared by the reversible addition–fragmentation chain transfer (RAFT) polymerization of *N*-isopropylacrylamide and an iridium complex monomer using a poly(*N,N*-dimethylacrylamide) macro-chain transfer agent (CTA) in the presence of a divinyl crosslinker. The resulting CD gel showed catalytic activity for the *N*-alkylation of aniline with benzyl alcohol, and importantly, the steric effect of the CD structure allowed the selective formation of a secondary amine product by controlling the access of the substrate to the iridium complex. Thus, we demonstrated selectivity control through the design of the nanospace surrounding the catalytic center using a nanostructured amphiphilic gel.

Polymer gels are attractive materials for various applications due to their unique properties derived from the combination of the solid component (polymer chains) and the liquid component (internal solvent). One of the intriguing uses of polymer gels is as carriers of functional molecules, taking advantage of their internal space and wet but insoluble nature [1, 2]. Gel catalysts containing organometallic complexes in the network structure are advantageous as heterogeneous catalysts that can be recovered and reused [3], and such gels have been studied for use in, for example, Suzuki–Miyaura coupling [4–6] and Au-catalyzed cyclization reactions [7]. Appropriate modification of the structure around the reactive sites and the affinity between the polymer chains and the substrates can improve the reactivity and reaction selectivity of a reaction system. However, there has been little progress in the development of novel gel catalysts based on the deliberate structural design of polymer gels.

The development of an advanced gel catalyst for highly selective reactions requires careful design and precise construction of the internal nanostructure of the polymer gel. We recently reported amphiphilic hydrogels with homogeneously dispersed crosslinked nanodomain (CD) structures [8–10]. This type of gel can comprise, for example, thermoresponsive CDs and hydrophilic polymer chains connecting the CDs, and such a gel exhibits characteristic swelling behavior in water and thermoresponsive mechanical toughening in air while maintaining its transparency and macroscopic volume. Furthermore, CD gels are useful for hybridization with functional molecules. One example is a CD gel containing fluorescent carbon dots, whose mechanical properties and photoluminescence simultaneously change in response to temperature changes [11]. Furthermore, we recently synthesized novel polymer gels hybridized with iridium complexes covalently incorporated

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41428-024-00885-x.

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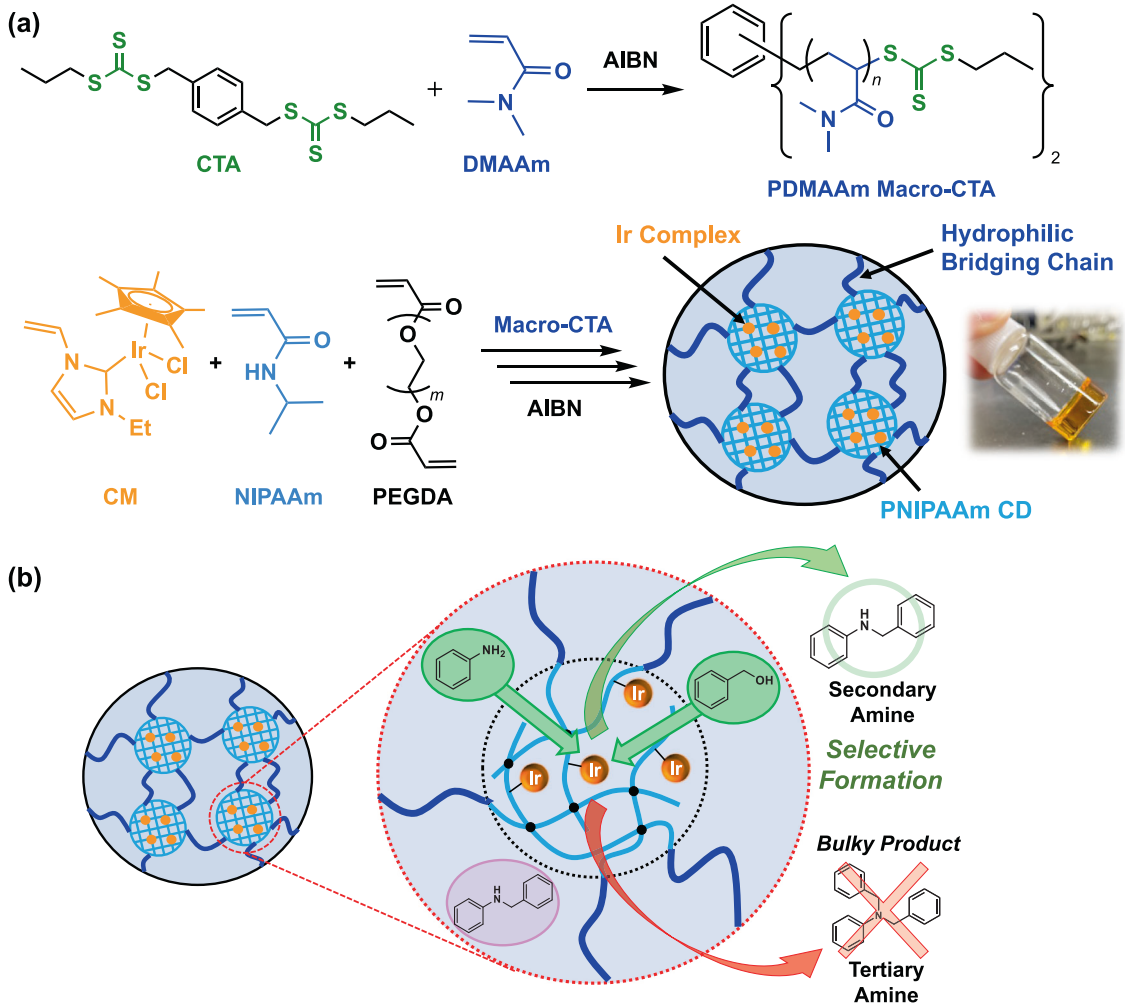


Fig. 1 **a** Synthetic scheme of an amphiphilic gel with a CD structure containing iridium complexes and **b** selectivity control of the catalytic *N*-alkylation of aniline with benzyl alcohol using a CD gel containing iridium complexes

into thermoresponsive CDs using designed iridium complex monomers (Fig. 1a) [12]. This type of polymer gel served as a visible-response molecular recognition material for ammonia molecules in water and showed potential catalytic activity for the *N*-alkylation of aniline with benzyl alcohol, but the latter has not been investigated in detail.

The iridium monomer investigated for incorporation into a CD gel in the previous report was based on a complex developed by Fujita et al. as an environmentally benign and green catalyst [13–18]. This complex consists of 1,2,3,4,5-pentamethylcyclopentadienyl (Cp*), *N*-heterocyclic carbene (NHC) and two labile halogen ligands and may be suitable for incorporation into hydrogels because of its high air and water stability. This complex is highly active in the *N*-alkylation of a primary amine compound with an alcohol, but this catalytic reaction sometimes produces not only a secondary amine product but also a tertiary amine byproduct because the secondary amine product can act as a nitrogen source in the alkylation reaction with an alcohol [13–18]. From the perspective of reaction selectivity, the design of the reaction site of an iridium catalyst is important for the suppression of such unfavorable reactions, and a hydrogel with a distinct nanospace is likely to be useful as a platform for preparing a metal catalyst for highly selective reactions.

In this work, we aimed to control the activity and selectivity of the catalytic *N*-alkylation of amine substrates with alcohols by varying the nanostructure of CD gels containing iridium complexes. In particular, we investigated the effect of the steric environment surrounding the complex on the catalytic reaction by controlling the size and crosslinking density of the CD structure in the gel (Fig. 1b).

First, we synthesized the poly(*N*,*N*-dimethylacrylamide) (PDMAAm) macro-chain transfer agent (macro-CTA) via reversible addition–fragmentation chain transfer (RAFT) polymerization using a bifunctional CTA, as shown in Fig. 1a [12] [degree of polymerization (DP_n) = 403 and number-average molecular weight (M_n) = 40,300, both of

which were calculated by ^{1}H nuclear magnetic resonance (NMR) analysis; polydispersity index (M_w/M_n) = 1.16, which was obtained by size-exclusion chromatography (SEC) measurements: Figs. S1 and S2 in the Supporting Information]. Then, the obtained macro-CTA was used in gel synthesis by the RAFT polymerization of *N*-isopropylacrylamide (NIPAAm) and an iridium complex monomer with chlorine ligands (**CM**) in the presence of polyethylene glycol diacrylate (PEGDA) as a crosslinker with various concentrations of DMAAm and NIPAAm monomers (Fig. 1a and Table 1). As shown in Table 1, all the conditions examined in this study successfully yielded gels regardless of the composition ratio (the obtained gels are denoted as **G$_{500}$**, **G$_{750}$** and **G$_{1000}$** according to the feed concentration of NIPAAm). For comparison, we synthesized a gel by the free radical copolymerization of NIPAAm and **CM** under the same NIPAAm and crosslinker concentration conditions as **G$_{1000}$** (this gel is denoted as **NG$_{1000}$**).

The internal structures of the product gels (**G$_{500}$**, **G$_{750}$** and **G$_{1000}$**) in the as-prepared state (internal solvent: DMF) were evaluated via small-angle X-ray scattering (SAXS) (Fig. S3 in the Supporting Information). The scattering profiles of the gels all showed a clear intensity maximum at a scattering vector (q) of ca. 0.2 nm^{-1}, indicating that all the gels have an electron-dense internal particle structure with almost constant distances (Table 1 and Table S1 in the Supporting Information). These results demonstrated that a homogeneously dispersed CD structure was formed in the obtained gels regardless of the composition ratio. The average distances D ($= 2\pi/q_{max}$) between the neighboring internal particles were determined for each gel, and from these values, the radii of the CDs (r_{CD}) were further calculated according to our previous report (Table S1 in the Supporting Information) [10]. The results showed that the gel with the lowest NIPAAm content (**G$_{500}$**) had a smaller CD (6.9 nm) than did **G$_{750}$** and **G$_{1000}$**, which had CDs of similar size (7.5 nm) (Table 1). A higher feed concentration of the NIPAAm monomer was likely to result in the formation of larger CDs, and at the same time, the number of macro-CTAs connected to one CD decreased. The balance of these factors is considered to determine the size of the CD structure. In addition, since the gels were prepared with a constant concentration of PEGDA crosslinker, the crosslinking density of the CD structure varied among the gels.

We subsequently estimated the amount of iridium complex monomer introduced into each CD gel by performing polymerization under the same monomer concentration conditions used for **G$_{500}$** and **G$_{750}$** but in the absence of the crosslinker (Scheme S1 and Table S2 in the Supporting Information; the model reaction for **G$_{1000}$** was reported in our previous study [12]). In this reaction, ABA triblock polymers with outer A blocks consisting of P(NIPAAm/**CM**) and inner B blocks consisting of PDMAAm were produced when controlled polymerization proceeds. The molecular weight distributions of the obtained polymers were relatively narrow, and the peak top apparently indicated a higher molecular weight than that of macro-CTA, although a slightly lower molecular weight compound was observed in the product from the high NIPAAm concentration condition (Fig. S4 in the Supporting Information). These results demonstrated that the polymerization of NIPAAm and **CM** proceeded in a controlled manner from both ends of the macro-CTA regardless of the monomer concentration. This controlled polymerization was likely to produce a homogeneously dispersed CD structure, as observed in the SAXS profiles (Fig. S3 in the Supporting Information). In addition, the ^{1}H NMR spectra (Figs. S5 and S6 in the Supporting Information), and the results of the elemental analysis and the inductively coupled plasma (ICP) analysis of the obtained polymers indicated an incorporation ratio of **CM** of approximately 60% (Table S2; the details of the calculations are presented in the Supporting Information). Thus, we confirmed the successful incorporation of the iridium complex by RAFT polymerization using PDMAAm macro-CTA.

Table 1 Synthesis and SAXS structural analysis of gels containing iridium complexes[a]

Gel Code[b]	[NIPAAm] (mM)	[DMAAm unit] (mM)	q_{max} (nm^{-1})[c]	D (nm)[d]	r_{CD} (nm)[e]
G$_{500}$	500	1500	0.22	28	6.9
G$_{750}$	750	1250	0.21	30	7.5
G$_{1000}$	1000	1000	0.21	30	7.5
NG$_{1000}$	1000	–	–	–	–

[a]Reaction conditions: [**CM**] = 15 mM; [PEGDA] = 20 mM; [AIBN] = 5.0 mM in DMF at 60 °C for 16 h

[b]The subscript number in the sample code represents the feed concentration of the NIPAAm monomer. G represents a gel with a CD structure, and NG represents a NIPAAm gel prepared by free radical polymerization

[c]Obtained from the SAXS profiles (Fig. S3 in the Supporting Information)

[d]The distance between CDs obtained from the SAXS profile ($= 2\pi/q_{max}$)

[e]The average radius of CDs, calculated from D and the end-to-end distance of PDMAAm with DP$_n$ = 403. The details of the calculation method are presented in Table S1 in the Supporting Information

The effect of the CD structure on the reactivity of the iridium-catalyzed *N*-alkylation of aniline with benzyl alcohol was investigated (Scheme 1 and Table 2). For comparison, reactions using an iridium-containing PNIPAAm gel without a CD structure, **NG$_{1000}$**, and the corresponding low-molecular-weight iridium complex (**IC** in Scheme 1) were also examined. Here, 2,2,2-trifluoroethanol (TFE) was used as the reaction solvent because TFE is a satisfactory

Scheme 1 *N*-alkylation of benzyl alcohol with aniline catalyzed by gel catalysts containing embedded iridium complexes

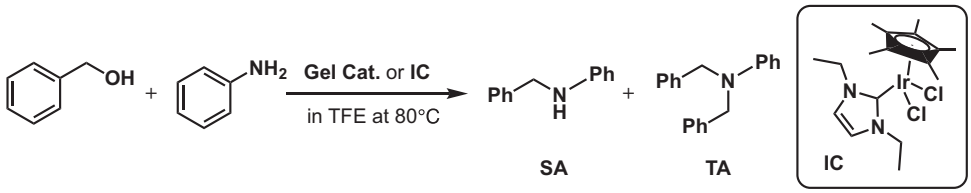


Table 2 Results of iridium-catalyzed *N*-alkylation[a]

Entry	Ir Catalyst	[benzyl alcohol]/[aniline]	Conv. (%)[b]	Yield of SA (%)[c]	Yield of TA (%)[c]
1	$\mathbf{G_{500}}$	1.0	11	1	0
2	$\mathbf{G_{750}}$	1.0	17	5	0
3	$\mathbf{G_{1000}}$	1.0	42	37	0
4	$\mathbf{NG_{1000}}$	1.0	99	60	14
5	$\mathbf{G_{500}}$	2.0	6	4	0
6	$\mathbf{G_{750}}$	2.0	10	8	0
7	$\mathbf{G_{1000}}$	2.0	29	52	0
8	$\mathbf{NG_{1000}}$	2.0	88	18	60
9[d]	**IC**	1.0	99	67	9
10[de]	**IC**	1.0	100	80	8
11[d]	**IC**	2.0	81	40	46

[a]Reaction conditions: 1.0 mmol of aniline in 1.0 mL of TFE at 80 °C for 100 h. Ir: 2.25 mol%

[b]Conversion of benzyl alcohol measured by GC analysis

[c]Measured by GC analysis. The yield was calculated as the value against aniline

[d]Feed Ir catalyst: 1.0 mol%. Reaction time: 20 h

[e]The reaction was conducted in the presence of CTA (0.13 mol%)

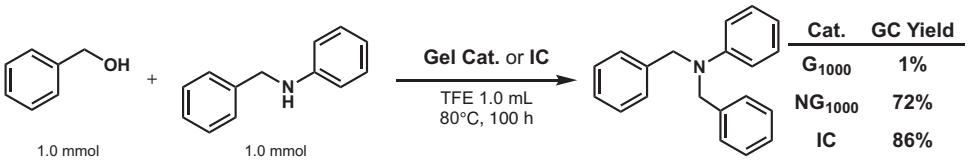
solvent for the gel (Table S3 in the Supporting Information) and a typical solvent for the catalytic reaction of similar iridium complexes [14]. With increasing mesh size of the CD (from $\mathbf{G_{500}}$ to $\mathbf{G_{1000}}$), the conversion of benzyl alcohol as a substrate and the yield of the desired secondary amine product, *N*-benzylaniline (SA), both increased (entries 1–3 in Table 2). This trend in reactivity is probably due to the easy access of the substrate to the catalytic active site in CDs with larger mesh sizes, such as $\mathbf{G_{1000}}$. Importantly, no tertiary amine, *N,N*-dibenzylaniline (TA), was generated during the reaction using CD gel catalysts, whereas $\mathbf{NG_{1000}}$, which has a looser network, produced a considerable amount of TA (entry 4 in Table 2; Fig. S7 in the Supporting Information). Similar behavior to that of $\mathbf{NG_{1000}}$ was observed in the homogeneous reaction with the corresponding small-molecule catalyst, **IC** (Entry 9). The formation of TA may be due to the further reaction of SA generated by the *N*-alkylation of aniline with benzyl alcohol, as shown in Schemes S2 and S3 in the Supporting Information. These results indicated that the confined internal nanospace of the CD structure may restrict the access of the secondary amine to the iridium catalyst, thereby providing high selectivity for the reaction product. Moreover, since the presence of CTA in the reaction system with **IC**s had only a slight effect on the reaction (entry 10), the reactivity in the CD gel system was likely dependent on the access of the substrate to the catalytic sites.

To further investigate the effect of the CD structure on the reaction selectivity, the reaction was conducted using twice the amount of benzyl alcohol (entries 5–8 and 11). Under these conditions, only SA was produced when using CD gels as a catalyst, whereas the yield of the byproduct TA increased in the $\mathbf{NG_{1000}}$ and **IC** systems. In the CD gel system, the yield of SA increased compared to that under equimolar conditions, and the effect of mesh size on the reactivity exhibited the same trend. In addition, we investigated the reaction using SA as the substrate with benzyl alcohol, as shown in Scheme 2. TA was rarely produced when $\mathbf{G_{1000}}$ was used, while the reactions using $\mathbf{NG_{1000}}$ and **IC** produced a high amount of TA. These results supported the above discussion that the confined space in the CD structure of the polymer gel sterically controlled the access of the substrate to the catalytic active site, thereby improving the product selectivity.

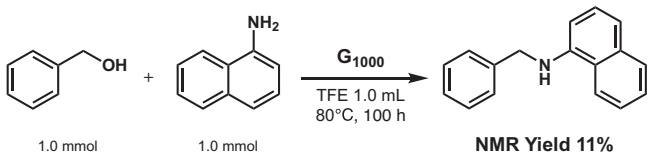
Finally, we investigated the reaction using 1-naphtylamine as the amine substrate with benzyl alcohol using $\mathbf{G_{1000}}$, as shown in Scheme 3. This reaction also produced only a secondary amine product, *N*-benzyl-1-naphtylamine. The yield (11%) was lower than that of the reaction with aniline, probably due to the bulkiness of 1-naphthylamine.

In summary, we investigated the control of the reactivity and selectivity of a catalytic reaction using designed gel catalysts with metal catalysts embedded in a confined nanostructure. For this purpose, we prepared various CD gels with different composition ratios by RAFT polymerization using macro-CTAs. Structural analysis via various measurements revealed that the product gels had homogeneously dispersed CD structures with various crosslinking densities containing iridium complexes. The results of the *N*-alkylation of aniline with benzyl alcohol using the designed CD gel catalysts demonstrated that the access of the substrate to catalytic sites is strongly controlled by the steric effect of the CD structure, resulting in the selective formation of a secondary amine product. Thus, we demonstrated selectivity control by designing nanospaces around the catalytic center using nanostructured amphiphilic gels, although there is still room to increase the

Scheme 2 *N*-alkylation of SA with benzyl alcohol by gel catalysts ($\mathbf{G_{1000}}$ and $\mathbf{NG_{1000}}$) and **IC** (Ir 2.25 mol%)



Scheme 3 *N*-alkylation of 1-naphylamine with benzyl alcohol by $\mathbf{G_{1000}}$ (Ir 2.25 mol%)



yield. In addition, since our design in the current study utilizes thermoresponsive PNIPAAm nanodomains, we believe that this gel catalyst system can be developed to obtain a more sophisticated system with high selectivity because of its stimuli-responsiveness.

Acknowledgements This work was partially supported by JST SPRING (Grant no. JPMJSP2110) and the Japan Society for the Promotion of Science through Grants-in-Aid for Scientific Research (C) (No. 19K05602) and (B) (No. 22H02075), for which the authors are grateful. The SAXS experiments at the Photon Factory were performed under the approval of the Photon Factory Program Advisory Committee (Proposal no. 2023G057).

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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